Vitamins

Español

The term vitamin is derived from the words vital and amine, because vitamins are required for life and were originally thought to be amines. Although not all vitamins are amines, they are organic compounds required by humans in small amounts from the diet. An organic compound is considered a vitamin if a lack of that compound in the diet results in overt symptoms of deficiency.

The information from the Linus Pauling Institute's Micronutrient Information Center on vitamins and minerals is now available in a book titled, *An Evidence-based Approach to Vitamins and Minerals: Health Benefits and Intake Recommendations*. The book can be purchased from the Linus Pauling Institute or Thieme Medical Publishers.

Select a vitamin from the list for more information.

- Biotin
- Folate
- Niacin
- Pantothenic Acid
- Riboflavin
- Thiamin
- Vitamin A
- Vitamin B_6
- Vitamin B_{12}
- Vitamin C
- Vitamin D
- Vitamin E
- Vitamin K

Biotin

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Summary

- Water-soluble biotin is an essential cofactor to enzymes in intermediary metabolism and a key regulator of gene expression. *(More information)*
- Both parenteral nutrition devoid of biotin and prolonged consumption of raw egg white have been associated with symptoms of frank biotin deficiency, including hair loss, dermatitis, skin rash, ataxia, seizures, and other neurologic dysfunctions. *(More information)*
- Biotinidase deficiency is a rare hereditary disorder that impairs biotin absorption and recycling, resulting in secondary biotin deficiency. *(More information)*
- The recommended adequate intake (AI) of biotin is set at 30 micrograms (μg)/day in adults. Biotin requirements are likely increased during pregnancy and breast-feeding. *(More information)*
- Animal studies have shown that biotin sufficiency is essential for normal fetal development. Yet, it is not known if marginal biotin deficiency during pregnancy increases the risk for congenital anomalies in humans. *(More information)*
- Biotin is used in the treatment of biotin-thiamin responsive basal ganglia disease, an inherited disorder of thiamin transport. *(More information)*
- Recent randomized controlled trials have not found high-dose biotin supplementation to be beneficial in the treatment of multiple sclerosis. Yet, results of animal studies and meta-analyses of human clinical trials are promising. *(More information)*
- Definitive evidence that establishes whether biotin supplementation improves glucose and lipid homeostasis in individuals with type 2 diabetes mellitus is currently lacking, but suggestive observations have been published. *(More information)*
- Biotin cannot be synthesized by mammalian cells and must be obtained from exogenous sources. Biotin is widely found in food, and good dietary sources include egg yolk, liver, whole-grain cereal, and some vegetables. *(More information)*
- Long-term anticonvulsant (anti-seizure) therapy may increase the dietary requirement for biotin because anticonvulsants can interfere with the intestinal absorption and renal re-absorption of biotin and likely also increase degradation of biotin to inactive metabolites. *(More information)*
- Use of high-dose biotin supplements can result in aberrant results of laboratory tests that utilize the very high affinity biotin-streptavidin (avidin) interaction. *(More information)*

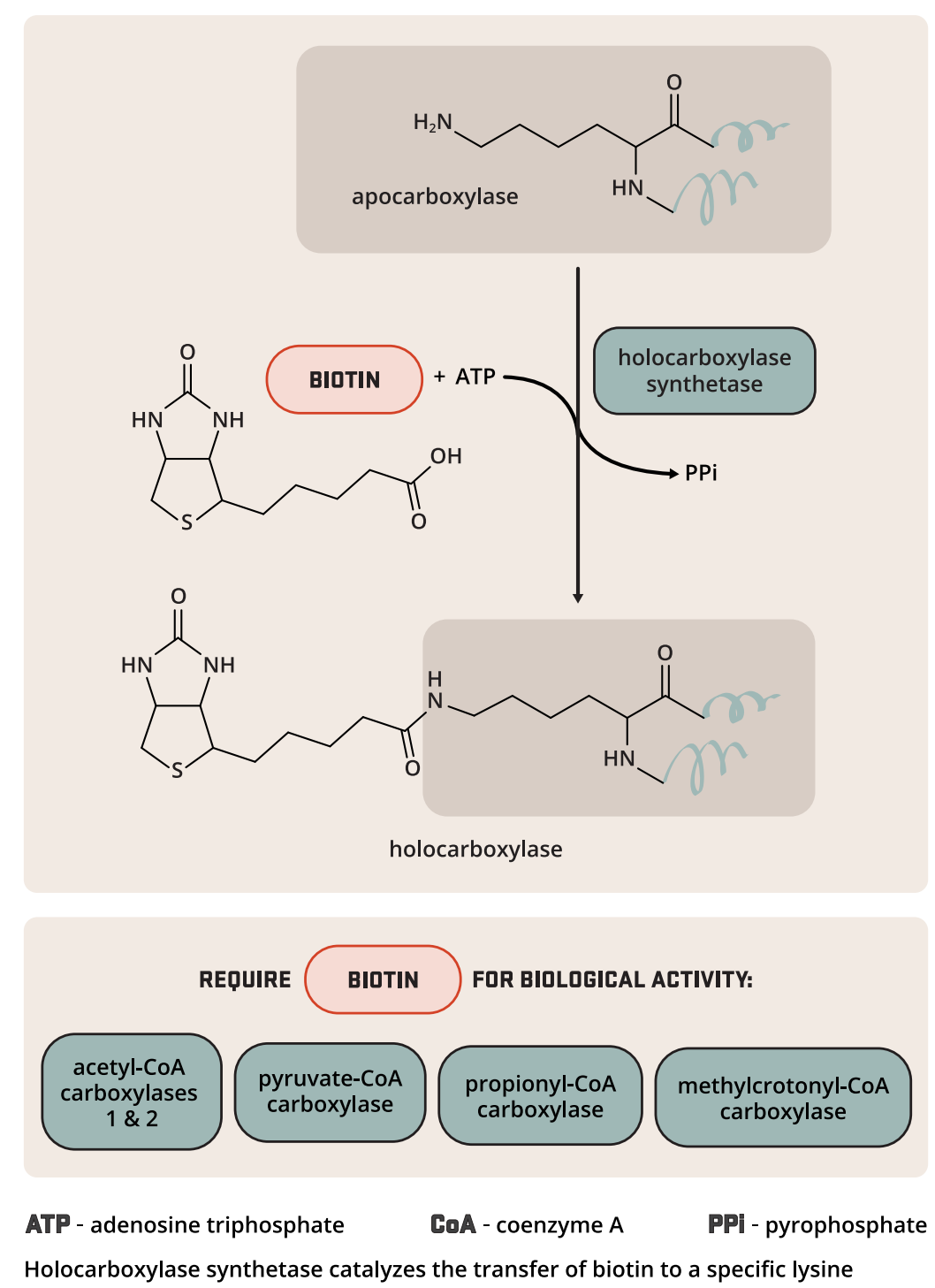
Biotin is a water-soluble vitamin that is generally classified as a B-complex vitamin. After its initial discovery in 1927, 40 years of additional research was required to unequivocally establish biotin as a vitamin (1). Biotin is required by all organisms but can be synthesized by some strains of bacteria, yeast, mold, algae, and some plant species (2).

Function

Biotinylation

Biotin functions as a covalently bound cofactor required for the biological activity of the five known mammalian biotin-dependent carboxylases (see below). Such non-protein cofactors are termed "prosthetic groups" and are common in water-soluble vitamins. The covalent attachment of biotin to the apocarboxylase (i.e., the carboxylase protein without the biotin prosthetic group and is catalytically inactive) is catalyzed by the enzyme, holocarboxylase synthetase (HCS). The term "biotinylation" refers to the covalent addition of biotin to any molecule, including the apocarboxylases and histones. HCS catalyzes the post-translational biotinylation of the epsilon amino group of a lysine residue at the active site of each apocarboxylase, converting the inactive apocarboxylase into a fully active holocarboxylase (**Figure 1a**). Particular lysine residues within the N-terminal tail of specific histone that help package DNA in eukaryotic nuclei can also be biotinylated (3). Biotinidase is the enzyme that catalyzes the release of biotin from biotinylated histones and from the peptide products of holocarboxylase breakdown (**Figure 1b**).

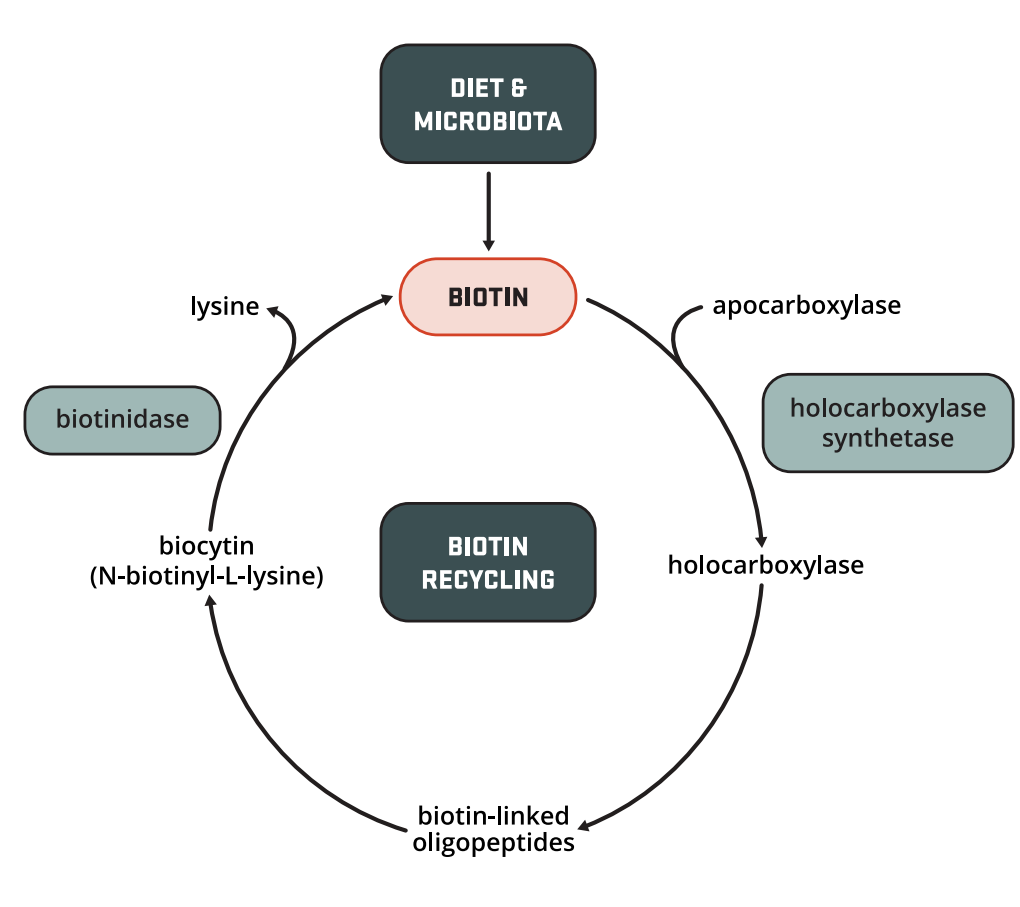
Figure 1a. Biotinylation of Carboxylases



H_2N
apocarboxylase
HN
BIOTIN
+ ATP
holocarboxylase synthetase
PPi
HN
NH
OH
S
O
holocarboxylase
REQUIRE BIOTIN FOR BIOLOGICAL ACTIVITY:
acetyl-CoA carboxylases 1 & 2
pyruvate-CoA carboxylase
propionyl-CoA carboxylase
methylcrotonyl-CoA carboxylase
ATP - adenosine triphosphate
CoA - coenzyme A
PPi - pyrophosphate

Holocarboxylase synthetase catalyzes the transfer of biotin to a specific lysine residue at the active site of apocarboxylase, converting the enzyme to a fully active holocarboxylase. Five mammalian carboxylases are known to require biotin for their biological activity: acetyl-CoA carboxylases 1 and 2, pyruvate-CoA carboxylase, propionyl-CoA carboxylase, and methylcrotonyl-CoA carboxylase.

Figure 1b. Biotin Recycling



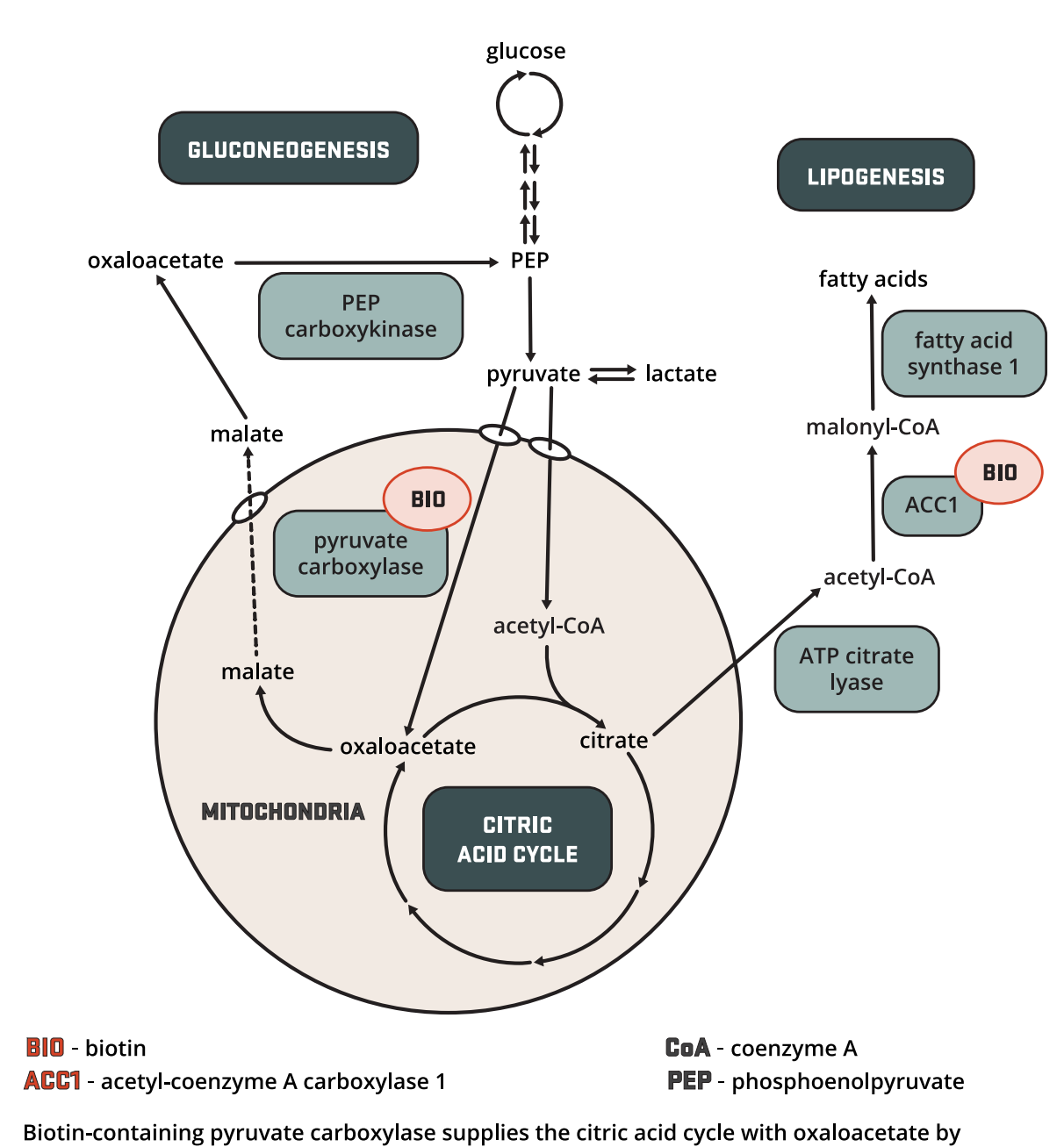
The biotinylation of apocarboxylase is catalyzed by holocarboxylase synthetase, while the enzyme biotinidase catalyzes the removal of biotin from the peptide products of carboxylase breakdown.

Enzyme cofactor

Five mammalian carboxylases catalyze essential metabolic reactions:

• Both **acetyl-Coenzyme A (CoA) carboxylase 1 (ACC1)** and **acetyl-CoA carboxylase 2 (ACC2)** catalyze the conversion of acetyl-CoA to malonyl-CoA using bicarbonate and ATP; however, the two enzymes have different roles in metabolism and different intracellular locations. ACC1 is located in the cytosol, and the malonyl CoA generated by ACC1 is a rate-limiting substrate for the synthesis of fatty acids (**Figure 2**). ACC1 is found in all tissues and is particularly active in lipogenic tissues (i.e., liver, white adipose tissue, and mammary gland), heart, and pancreatic islets. ACC2 is located on the outer mitochondrial membrane, and the malonyl CoA generated via ACC2 inhibits CPT1, an enzyme that regulates malonyl-CoA entry into the inner mitochondria, thereby regulating fatty acid oxidation (**Figure 3**). ACC2 is especially abundant in skeletal muscle and heart (4).

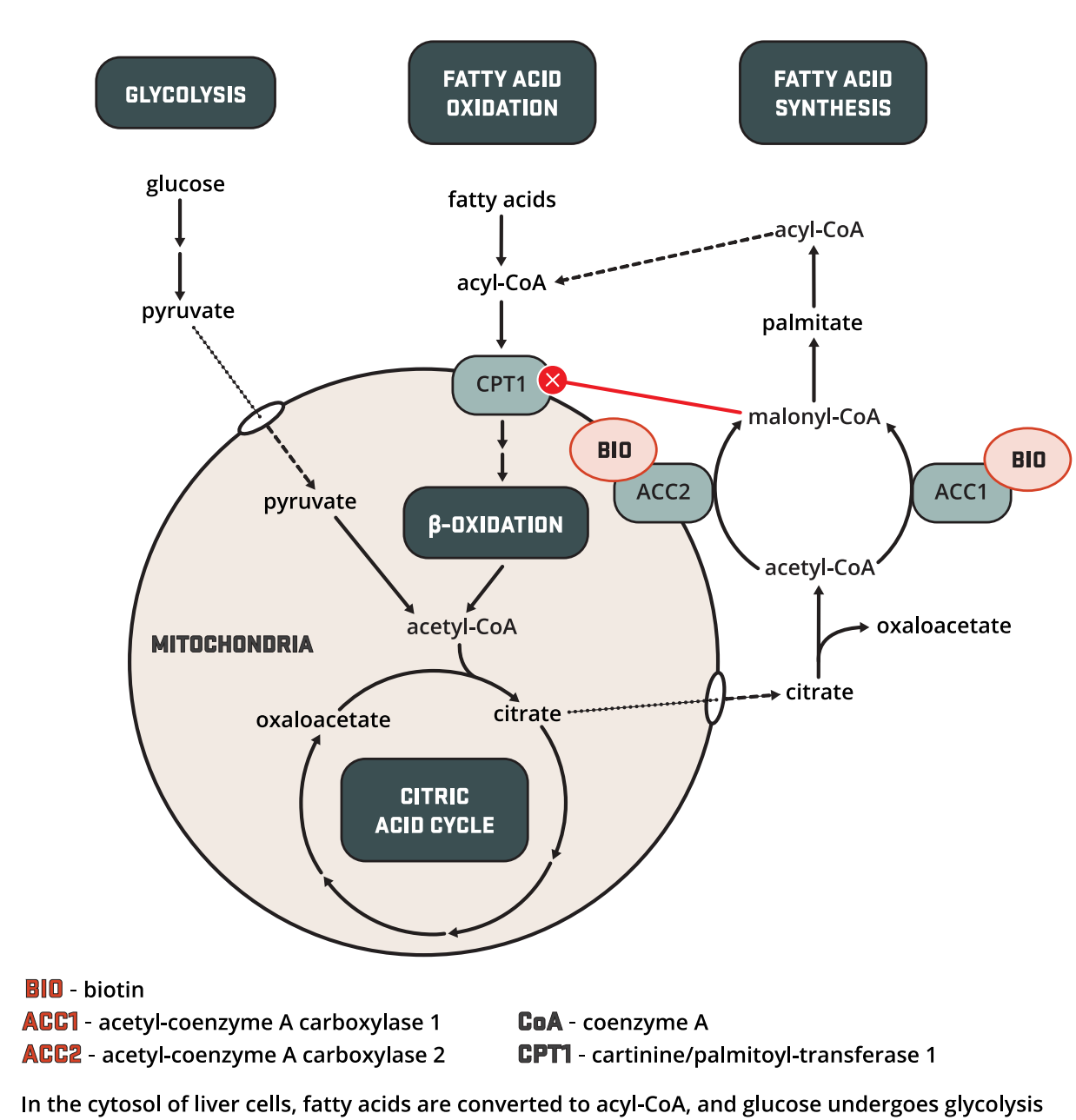
Figure 2. Pyruvate Carboxylase and Acetyl-CoA Carboxylase 1



Biotin-containing pyruvate carboxylase supplies the citric acid cycle with oxaloacetate by catalyzing the conversion of pyruvate to oxaloacetate using bicarbonate and ATP. In the liver, oxaloacetate can be used as a precursor for gluconeogenesis. It is first converted to phosphoenolpyruvate (PEP) by PEP carboxykinase and then to glucose via the reverse pathway of glycolysis. In the citric acid cycle, oxaloacetate can also be condensed with acetyl-CoA to produce citrate, which can be exported from the mitochondria. In the liver, adipose tissue, and skeletal muscle, citrate is cleaved to oxaloacetate and acetyl-CoA in the cytosol. Acetyl-CoA is converted to malonyl-CoA by another biotin-containing enzyme, acetyl-CoA carboxylase 1. Malonyl-CoA is then used by fatty acid synthase 1 to generate long-chain fatty acids.

• **Pyruvate carboxylase** is a critical enzyme in gluconeogenesis (the formation of glucose from sources other than carbohydrates, such as pyruvate, lactate, glycerol, and the glucogenic amino acids). Pyruvate carboxylase catalyzes the ATP-dependent incorporation of bicarbonate into pyruvate, producing oxaloacetate; hence, pyruvate carboxylase is anaplerotic for the citric acid cycle (**Figure 3**). Oxaloacetate can then be converted to phosphoenolpyruvate and eventually to glucose.

Figure 3. Acetyl-CoA Carboxylase 1 and Acetyl-CoA Carboxylase 2

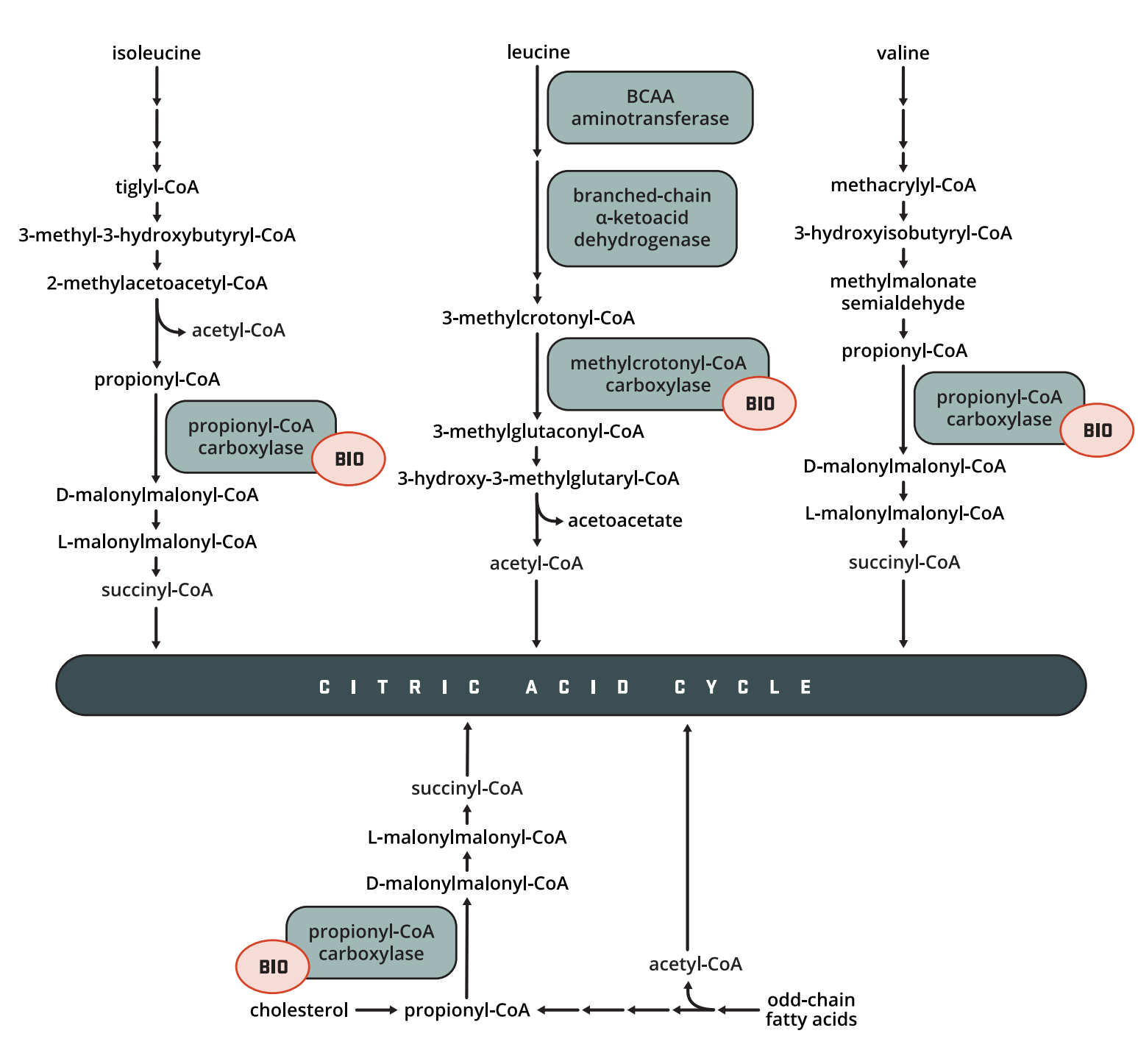


In the cytosol of liver cells, fatty acids are converted to acyl-CoA, and glucose undergoes glycolysis that produces pyruvate. Acyl-CoA is shuttled into the mitochondria via CPT1-mediated transport and undergoes β-oxidation that generates acetyl-CoA. In addition, pyruvate is converted to acetyl-CoA in the mitochondria, and acetyl-CoA is condensed with oxaloacetate to form citrate. The latter can be exported to the cytosol and cleaved to oxaloacetate and acetyl-CoA. Acetyl-CoA is used to generate malonyl-CoA in a reaction catalyzed by biotin-containing acetyl-CoA carboxylase 1 (ACC1) in the presence of ATP and bicarbonate. Malonyl-CoA is an essential substrate for the biosynthesis of fatty acids and subsequent triglycerides, phospholipids, and lipoproteins. Malonyl-CoA is also a regulator of fatty acid β-oxidation. Indeed, malonyl-CoA generated from acetyl-CoA by another biotin-containing enzyme, acetyl-CoA carboxylase 2 (ACC2), localized at the mitochondrial membrane, has been shown to downregulate fatty acid β-oxidation in the mitochondria by inhibiting CPT1.

• **Methylcrotonyl-CoA carboxylase** catalyzes an essential step in the catabolism of leucine, an essential branched-chain amino acid. This enzyme catalyzes the production of 3-methylglutaconyl-CoA from methylcrotonyl-CoA (**Figure 4a**).

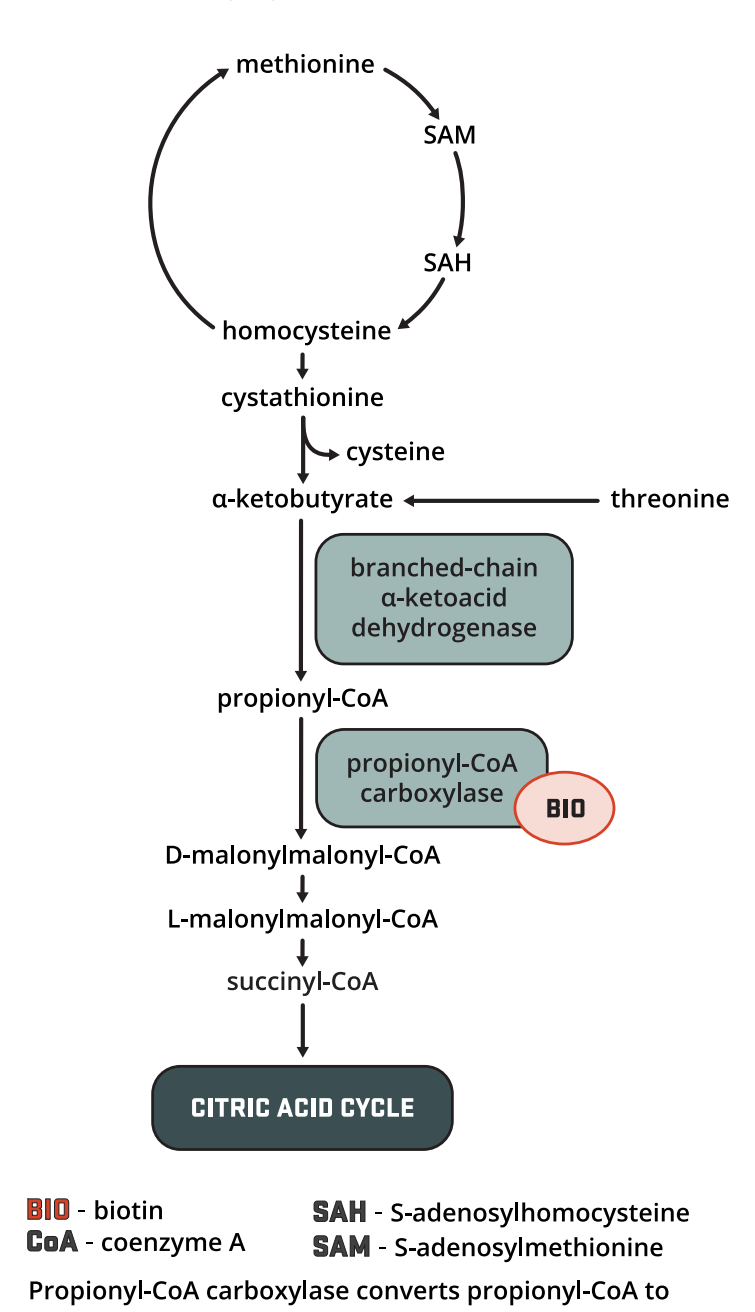
• **Propionyl-CoA carboxylase** produces D-malonylmalonyl-CoA from propionyl-CoA, a by-product in the β-oxidation of fatty acids with an odd number of carbon atoms (**Figure 4a**). The conversion of propionyl-CoA to D-malonylmalonyl-CoA is also required in the catabolic pathways of two branched-chain amino acids (isoleucine and valine) and the side chain of cholesterol (**Figure 4a**) and of the amino acids methionine and threonine (**Figure 4b**).

Figure 4a. Biotin-containing Carboxylases in the Metabolism of BCAAs, Odd-Chain Fatty Acids, and Cholesterol



Two biotin-containing enzymes, namely propionyl-CoA carboxylase and methylcrotonyl-CoA carboxylase, are required in the metabolism of branched-chain amino acids (leucine, valine, and isoleucine), the oxidation of odd-chain fatty acids, and the degradation of cholesterol side chain. The metabolic pathways generate acetyl-CoA and succinyl-CoA, which then enter the citric acid cycle.

Figure 4b. Biotin-containing Propionyl-CoA Carboxylase in the Metabolism of Methionine and Threonine



Propionyl-CoA carboxylase converts propionyl-CoA to D-malonylmalonyl-CoA in the metabolism of methionine and threonine.

Regulation of chromatin structure and gene expression

In eukaryotic nuclei, DNA is packaged into compact structures to form nucleosomes — fundamental units of chromatin. Each nucleosome is composed of 147 base pairs of DNA wrapped around eight histones (paired histones: H2A, H2B, H3, and H4). The H1 linker histone is located at the outer surface of each nucleosome and serves as an anchor to fix the DNA around the histone core. The compact packaging of chromatin must be relaxed for DNA replication and transcription. Chemical modifications of DNA and histones affect the folding of chromatin, increasing or reducing DNA accessibility to factors involved in replication and transcription. DNA methylation and a number of chemical modifications within the N-terminal tail of core histones modify their electric charge and structure, thereby changing chromatin conformation and transcriptional activity of genes.

The modifications of histone tails ("marks"), including acetylation, methylation, phosphorylation, ubiquitination, SUMOylation, ADP-ribosylation, carbonylation, deimination, hydroxylation, and biotinylation, have various regulatory functions. Several sites of biotinylation have been identified in histones H2A, H3, and H4 (5). Amongst them, histone H4 biotinylation at lysine (K) 12 (noted H4K12bio) appears to be enriched in heterochromatin, a tightly condensed chromatin associated with repeat regions in (peri)centromeres and telomeres. H4 biotinylation appears to be enriched in transposable elements known as long terminal repeats (3). These biotinylation marks also co-localize with well-known gene repression marks like methylated lysine 9 in histone H3 (H3K9me) in transcriptionally competent chromatin (6). For example, H4K12bio can be found at the promoter of the gene *SLC5A6* that codes for the transporter mediating biotin uptake into cells, the human sodium-dependent multivitamin transporter (hSMVT). When biotin is abundant, HCS can biotinylate histones H4 in the *SLC5A6* promoter, which down regulates hSMVT synthesis and reduces biotin uptake. Conversely, in biotin-deficient cells, biotinylation marks in the *SLC5A6* promoter are removed increasing gene expression and enabling the synthesis of hSMVT and uptake of biotin (7).

Deficiency

Although clinically overt biotin deficiency is very rare, the human requirement for dietary biotin has been demonstrated in three different situations: prolonged intravenous feeding (parenteral) without biotin supplementation, infants fed an elemental formula devoid of biotin, and consumption of raw egg white for a prolonged period (many weeks to years) (8). Raw egg white contains avidin; this antimicrobial protein binds biotin with an affinity and specificity that is almost unique as a reversible binding. Because native avidin is resistant to mammalian and microbial digestion, avidin prevents biotin absorption. Cooking egg white denatures avidin, rendering it susceptible to digestion and therefore unable to block the absorption of dietary biotin (5).

Signs and symptoms of biotin deficiency

Signs of overt biotin deficiency include hair loss (alopecia) and a scaly red rash around the eyes, nose, mouth, and genital area. Neurologic symptoms in adults have included depression, lethargy, hallucinations, numbness and tingling of the extremities, ataxia, and seizures. The characteristic facial rash, together with unusual facial fat distribution, has been termed the "biotin deficient facies" by some investigators (1). Individuals with hereditary disorders of biotin metabolism (see Inborn metabolic disorders) that result in functional biotin deficiency often have similar physical findings, impaired immune system function, and increased susceptibility to bacterial and fungal infections (9, 10).

Risk factors for biotin deficiency

Aside from prolonged consumption of raw egg white or total intravenous nutritional support lacking biotin, other conditions may increase the risk of biotin depletion. Smoking has been associated with increased biotin catabolism (11). The rapidly dividing cells of the developing fetus require biotin for synthesis of essential carboxylases and for histone biotinylation; hence, the maternal biotin requirement is likely increased during pregnancy. Research suggests that a substantial number of women develop marginal or subclinical biotin deficiency during normal pregnancy (see also Disease Prevention) (8, 12, 13). Moreover, certain types of liver disease may decrease biotinidase activity and theoretically increase the requirement for biotin. For example, a study of 62 children with chronic liver disease and 27 healthy controls found serum biotinidase activity to be abnormally low in those with severely impaired liver function due to cirrhosis (14). However, this study did not provide evidence of biotin deficiency. Additionally, anticonvulsant medications used to prevent seizures in individuals with epilepsy increase the risk of biotin depletion (for more information on biotin and anticonvulsants, see Drug interactions).

Inborn metabolic disorders

Biotinidase deficiency

Biotinidase deficiency is an autosomal recessive inherited disorder that is often detected upon newborn screening for metabolic disorders, although late-onset forms have been recently described (15-17). Biotinidase deficiency leads to secondary biotin deficiency in several ways. Intestinal absorption is decreased because deficient biotinidase impairs release of biotin from dietary protein (18). Further, recycling of intracellular biotin bound to carboxylases and histones is also impaired, and urinary loss of biocytin (*N*-biotinyl-lysine) and biotin is increased (see **Figure 1** above) (5). Biotinidase deficiency responds to supplemental biotin. Oral supplementation with as much as 5 to 20 milligrams (mg) of biotin daily is sometimes required (19, 20), although smaller doses may be sufficient, especially later in childhood (reviewed in 20, 21). Prognosis is characteristically good when biotin therapy is introduced in infancy or early childhood and reliably continued for life (10).

Holocarboxylase synthetase deficiency

Holocarboxylase synthetase deficiency results in decreased formation of all holocarboxylases at physiological blood biotin concentrations; thus, high-dose biotin supplementation (10-80 mg of biotin daily) is required (10). Holocarboxylase synthetase deficiency responds to supplementation with pharmacologic doses of biotin in some cases but not others. The prognosis of holocarboxylase synthetase is usually, but not always, good if biotin therapy is introduced early (even antenatally) and continued for life (10, 22).

Biotin transport deficiency

There has been one case report of a child with biotin transport deficiency who responded to high-dose biotin supplementation (23). Of note, the presence of a defective human sodium-dependent multivitamin transporter (hSMVT) was ruled out as a cause of biotin transport deficiency.

Markers of biotin status

Four measures of marginal biotin deficiency have been validated as indicators of biotin status: and (1) reduced levels of holo-methylcrotonyl-CoA carboxylase and holo-propionyl-CoA carboxylase in lymphocytes, the most reliable indicators of biotin status (24); (2) reduced propionyl-CoA carboxylase activity in peripheral blood lymphocytes (5); (3) high urinary excretion of an organic acid, 3-hydroxyisovaleric acid, and its derivative, 3-hydroxyisovaleryl carnitine, both of which reflect decreased activity of biotin-dependent methylcrotonyl-CoA carboxylase; (4) reduced urinary excretion of biotin and some of its catabolites. These markers have been only validated in men and nonpregnant women, and they may not accurately reflect biotin status in pregnant or breast-feeding women (12, 25).

The Adequate Intake (AI)

Sufficient scientific evidence is lacking to estimate the dietary requirement for biotin; thus, no Recommended Dietary Allowance (RDA) for biotin has been established. Instead, the Food and Nutrition Board of the National Academy of Medicine set recommendations for an Adequate Intake (AI; **Table 1**). The AI for adults (30 μg/day) was extrapolated from the AI for infants exclusively fed human milk and probably overestimates the dietary requirement for biotin for most adults. Dietary intakes of generally healthy adults have been estimated to be 40 to 60 micrograms (μg) of biotin daily (1). The requirement for biotin in pregnancy may be increased (26).

Table 1. Adequate Intake (AI) for Biotin

Life Stage	Age	Males (μg/day)	Females (μg/day)
Infants	0-6 months	5	5
Infants	7-12 months	6	6
Children	1-3 years	8	8
Children	4-8 years	12	12
Children	9-13 years	20	20
Adolescents	14-18 years	25	25
Adults	19 years and older	30	30
Pregnancy	all ages	-	30
Breast-feeding	all ages	-	35

Disease Prevention

Congenital anomalies

Current research indicates that at least one-third of women develop marginal biotin deficiency during pregnancy (8). Small observational studies in pregnant women have reported an abnormally high urinary excretion of 3-hydroxyisovaleric acid in both early and late pregnancy, suggesting decreased activity of biotin-dependent methylcrotonyl-CoA carboxylase (27, 28). In a randomized, single-blinded intervention study in 26 pregnant women, supplementation with 300 μg/day of biotin for two weeks limited the excretion of 3-hydroxyisovaleric acid compared to placebo, confirming that increased 3-hydroxyisovaleric acid excretion indeed reflected marginal biotin deficiency in pregnancy (29). A small cross-sectional study in 22 pregnant women reported an incidence of low lymphocyte propionyl-CoA carboxylase activity greater than 80% (13). Although these levels of biotin deficiency are not associated with overt signs of deficiency in pregnant women, such observations are sources of concern because subclinical biotin deficiency has been shown to cause cleft palate and limb hypoplasia in several animal species (reviewed in 13). In addition, biotin depletion has been found to suppress the expression of biotin-dependent carboxylases, remove biotin marks from histones, and decrease the proliferation in human embryonic palatal mesenchymal cells in culture (30). Impaired carboxylase activity may result in alterations in lipid metabolism, which have been linked to cleft palate and skeletal abnormalities in animals. Further, biotin deficiency leading to reduced histone biotinylation at specific genomic loci may increase genomic instability and result in chromosome anomalies and fetal malformations (13).

Analogous to pregnant women who are advised to consume supplemental folic acid prior to and during pregnancy to prevent neural tube defects (see Folate), it would also be prudent to ensure adequate biotin intake throughout pregnancy. The current AI for pregnant women is 30 μg/day of biotin, and no toxicity has ever been reported at this level of intake (see Safety).

Disease Treatment

Biotin-thiamin-responsive basal ganglia disease

Biotin-thiamin-responsive basal ganglia disease (also called biotin-responsive basal ganglia disease, thiamin transporter-2 deficiency, and thiamin metabolism dysfunction syndrome-2) is caused by an autosomal recessive mutation in the *SLC19A3* gene that codes for thiamin transporter-2 (THTR-2). The disease usually presents around 3 to 10 years of age (31), but an early infantile form of the disease exists with onset as early as one month of age (32). Clinical features include subacute encephalopathy (confusion, drowsiness, altered level of consciousness), ataxia, and seizures.

A retrospective study of 18 affected individuals from the same family or the same tribe in Saudi Arabia showed that biotin monotherapy (5-10 mg/kg/day) efficiently abolished the clinical manifestations of the disease, although one-third of the patients suffered from recurrent acute crises. Often associated with poor outcomes, acute crises were not observed after thiamin supplementation started (300-400 mg/day) and during a five-year follow-up period, early diagnosis and immediate treatment with biotin and thiamin led to positive outcomes (33). Although the specific mechanism for therapeutic effects of biotin in biotin-thiamin-responsive basal ganglia disease remains unknown, lifelong high-dose supplementation with a combination of biotin and thiamin is the recommended treatment (31). Early diagnosis and treatment is important to ensure a better prognosis (32, 34).

Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune disease characterized by progressive damage to the myelin sheath surrounding nerve fibers (axons) and neuronal loss in the brain and spinal cord of affected individuals in anatomic locations that vary widely among affected individuals producing variable signs and symptoms. The progression of neurologic disabilities in MS patients is often assessed by the Expanded Disability Status Scale (EDSS) with scores from 1 to 10, from minimal signs of motor dysfunction (score of 1) to death by MS (score of 10). ATP deficiency due to mitochondrial dysfunction and increased oxidative stress may be partly responsible for the progressive degeneration of neurons in MS (35). Given its role in energy production by intermediary metabolism and fatty acid oxidation and in fatty acid synthesis (required for myelin formation) (see Function), high-dose biotin supplementation it has been hypothesized that to exert beneficial effects that would limit or reverse MS-associated functional impairments (35).

The mechanism of action of high-dose biotin has been investigated in a genetic mouse model of chronic axon injury caused by oxidative damage and bioenergetic failure. High-dose biotin restored redox homeostasis, mitochondria biogenesis, and ATP levels, and reversed axonal death and locomotor impairment. Dysregulation of the transcriptional program for lipid synthesis and degradation in the spinal cord was also normalized, possibly as the result of hyperactivation of a nutrient/energy/redox sensor that controls protein synthesis restoring lipid homeostasis.

A nonrandomized, uncontrolled pilot study in 23 patients with progressive MS found high doses of biotin (100-600 mg/day) to be associated with sustained clinical improvements in five (out of five) patients with progressive visual loss and 16 (out of 18) patients with partial paralysis of the limbs after a mean three months following treatment onset (36). Additionally, a multicenter, randomized, placebo-controlled trial in 154 subjects with progressive MS reported that 13 out of 103 patients supplemented with high-dose, pharmaceutical-grade biotin (300 mg/day) for 12 months achieved MS-related disability reversal — assessed by improved EDSS or 25-foot walk time (37). In comparison, none of the 51 patients randomized to the placebo group showed significant clinical improvements (37). However, when this regimen of high-dose biotin supplementation was examined in a larger, international cohort of patients with progressive MS (326 patients receiving biotin and 316 patients receiving placebo), no benefits on EDSS or walk time were seen after 12 months (38). Moreover, a randomized, double-blind, placebo-controlled trial in 93 MS patients with chronic visual loss found that 300 mg/day of pharmaceutical-grade biotin for six months did not improve visual acuity, but an interesting trend favoring the biotin group was observed in the subgroup of patients with progressive optic neuritis (39). Moreover, a meta-analysis of three randomized controlled trials (2 on disability; 3 on adverse effects), involving 889 individuals diagnosed with MS (the preponderance of participants [830] had progressive MS while only 59 had remitting relapsing MS) was conducted (40). Pooling results of two trials found no benefit of high-dose biotin on MS-related disability, but there was significant heterogeneity between the trials. When the subgroup progressive MS was analyzed separately, a moderate certainty of evidence suggested a potential benefit in favor of high-dose biotin for the 25-foot minute walk time (40). On balance, studies remain inconclusive but promising.

Diabetes mellitus

Overt biotin deficiency has been shown to impair glucose utilization in mice (41) and cause fatal hypoglycemia in chickens. Overt biotin deficiency likely also causes abnormalities in glucose regulation in humans (see Function). One early human study reported lower serum biotin concentrations in 43 patients with type 2 diabetes mellitus compared to 64 control subjects without the disease; an inverse relationship between fasting blood glucose and biotin concentrations was observed as well (42). In a small, randomized, placebo-controlled intervention study in 28 patients with type 2 diabetes, daily supplementation with 9 milligrams (mg) of biotin for one month resulted in a 45% decrease in mean fasting blood glucose concentrations (42). Yet, another small study in 10 patients with type 2 diabetes and 7 controls without diabetes found no effect of biotin supplementation (15 mg/day) for 28 days on fasting blood glucose concentrations in either group (43). A more recent double-blind, placebo-controlled study by the same research group showed that the same biotin regimen lowered plasma triglyceride concentrations in patients with hypertriglyceridemia — independent of whether they had type 2 diabetes (44). In this study, biotin administration did not affect blood glucose concentrations in either patient group. Additionally, a few studies have shown that co-supplementation with biotin and chromium picolinate may be a beneficial adjunct therapy in patients with type 2 diabetes (45-48). For information on chromium supplementation as a monotherapy for type 2 diabetes, see the article on Chromium.

Potential mechanisms for the glucose and lipid effects have been suggested. As a cofactor of carboxylases required for fatty acid synthesis, biotin may increase the utilization of glucose for fat synthesis. Also, biotin stimulates glucokinase, a liver enzyme that increases synthesis of glycogen, the storage form of glucose. Biotin also triggers the secretion of insulin in the pancreas of rats and improves glucose homeostasis (50). Yet, reduced activity of ACC1 and ACC2 would be expected to reduce fatty acid synthesis and increase fatty acid oxidation, respectively. Hence, whether pharmacologic doses of biotin benefits the management of hyperglycemia in patients with impaired glucose tolerance remains unclear. Moreover, whether supplemental biotin lowers the risk of cardiovascular complications in patients with diabetes by reducing serum triglycerides and LDL-cholesterol remains to be proven (44-46).

Brittle fingernails (onychorrhexis)

The finding that biotin supplements were effective in treating hoof abnormalities in hoofed animals suggested that biotin might also be helpful in strengthening brittle fingernails in humans (50-52). Three uncontrolled trials examining the effects of biotin supplementation (2.5 mg/day for several months) in women with brittle fingernails have been published (53-55). In two of the trials, subjective evidence of clinical improvement was reported in 67%-91% of the participants available for follow-up at the end of the treatment period (53, 54). One trial that used scanning electron microscopy to assess fingernail brittleness reported less fingernail splitting and a 25% increase in the thickness of the nail plate in patients supplemented with biotin for 6 to 15 months (55). Biotin supplementation (5 mg/day) was also found to be effective in controlling unruly hair and splitting nails in two toddlers with inherited uncombable hair syndrome (56). Although preliminary evidence suggests that supplemental biotin may help strengthen fragile nails (reviewed in 57), larger placebo-controlled trials are needed to assess the efficacy of high-dose biotin supplementation for the treatment of brittle fingernails.

Hair loss (alopecia)

Biotin administration has been associated with alopecia reversal in children treated with the anticonvulsant valproic acid (see Drug interactions), as well as with hair regrowth or normal hair growth in some children with inborn errors of biotin metabolism or other genetic disorders (i.e., uncombable hair syndrome) (reviewed in 58). Yet, while hair loss is a symptom of severe biotin deficiency (see Deficiency), there are no published scientific studies that support the claim that high-dose biotin supplements are effective in preventing or treating hair loss in men or women (59, 60). Randomized, placebo-controlled trials in healthy individuals would be needed to evaluate this claim.

Sources

Food sources

Biotin is found in many foods, either as the free (i.e., unbound) form that is directly taken up by enterocytes or as biotin bound to dietary proteins. Egg yolk, liver, and yeast are rich sources of biotin. Estimates of average daily intakes of biotin from small studies ranged between 40 and 60 micrograms (μg) per day in adults (1). However, US national nutritional surveys have not yet been able to estimate biotin intake due to the scarcity and unreliability of data regarding biotin content of food. Food composition tables for biotin are incomplete such that dietary intakes cannot be reliably estimated in humans. A study by Staggs et al. (61) employed a high-performance liquid chromatography method rather than bioassays (62) and reported relatively different biotin content for some selected foods. **Table 2** lists some food sources of biotin, along with their content in μg.

Table 2. Some Food Sources of Biotin (61, 62)

Food	Serving	Biotin (μg)
Yeast	1 packet (7 grams)	1.4-14
Bread, whole-wheat	1 slice	0.02-6
Egg, cooked	1 large	13-25
Cheese, cheddar	1 ounce	0.4-2
Liver, cooked	3 ounces*	27-35
Pork, cooked	3 ounces*	2-4
Salmon, cooked	3 ounces*	4-5
Avocado	1 whole	2-6
Raspberries	1 cup	0.2-2
Cauliflower, raw	1 cup	0.2-4
*A three-ounce serving of meat is about the size of a deck of cards.		

Bacterial synthesis

A majority of bacteria that normally colonize the small and large intestine (colon) synthesize biotin (63). Whether the biotin is released and absorbed by humans in meaningful amounts remains unknown. The uptake of free biotin into intestinal cells via the human sodium-dependent multivitamin transporter (hSMVT) has been identified in cultured cells derived from the lining of the small intestine and colon (64), suggesting that humans may be able to absorb biotin produced by enteric bacteria — a phenomenon documented in swine.

Supplements

Biotin is available as a single-nutrient supplement in various doses (many containing 5,000 μg [5 mg] of biotin) and is often included in B-complex and multivitamin-mineral supplements. Several multivitamin supplements contain 30 μg of biotin, although the amount varies by product (65).

Safety

Toxicity

Biotin is not known to be toxic. In people without disorders of biotin metabolism, doses of up to 5 mg/day (5,000 μg) for two years were not associated with adverse effects (66). Oral biotin supplementation has been well tolerated in doses up to 200 mg/day (nearly 7,000 times the AI) in people with hereditary disorders of biotin metabolism (1). Daily supplementation with a highly concentrated formulation of biotin (100-600 mg) for several months was also found to be well tolerated in individuals with progressive multiple sclerosis (36, 67). However, there is one case report of life-threatening eosinophilic pleuropericardial effusion in an elderly woman who took a combination of 10 mg/day of biotin and 300 mg/day of pantothenic acid (vitamin B_5) for two months (68). Because reports of adverse events were lacking when the Dietary Reference Intakes (DRIs) for biotin were established in 1998, the Food and Nutrition Board did not establish a tolerable upper intake level (UL) for biotin (1).

Nutrient interactions

Large doses of pantothenic acid (vitamin B_5) have the potential to compete with biotin for intestinal and cellular uptake by the human sodium-dependent multivitamin transporter (hSMVT) (69, 70). Biotin also shares the hSMVT with lipoic acid (71). Pharmacologic (very high) doses of lipoic acid have been found to decrease the activity of biotin-dependent carboxylases in rats, but such an effect has not been demonstrated in humans (72).

Drug interactions

Individuals on long-term anticonvulsant (anti-seizure) therapy reportedly have reduced blood biotin concentrations, as well as an increased urinary excretion of organic acids (e.g., 3-hydroxyisovaleric acid) that indicate decreased carboxylase activity (see Markers of biotin status) (5). Potential mechanisms of biotin depletion by the anticonvulsants, primidone (Mysoline), phenytoin (Dilantin, Phenytek), and carbamazepine (Carbatrol, Epitol, Equetro, Tegretol), include inhibition of biotin intestinal absorption and renal reabsorption, as well as increased biotin catabolism (73). Use of the anticonvulsant valproic acid in children has resulted in hair loss reversed by biotin supplementation (74-77). Long-term treatment with antibacterial sulfonamide (sulfa) drugs or other antibiotics may decrease bacterial synthesis of biotin. Yet, given that the extent to which bacterial synthesis contributes to biotin intake in humans is not known, effects of antimicrobial drugs on biotin nutritional status remain uncertain (73).

Interference with lab assays

In 2017, the US Food and Drug Administration (FDA) released a safety communication regarding high-dose biotin supplementation and its potential interference with streptavidin (avidin)-biotin immunoassays, including assays of thyroid hormones, reproductive hormones, and the cardiac protein, troponin. Such interference can cause aberrant results — either falsely high or falsely low depending on the method of the particular assay — and potential misdiagnosis of disease (78-81). An updated FDA communication in 2019 focused on biotin interference in certain lab assays of troponin that have not addressed the concern of falsely low blood concentrations (82). Troponin in blood is a marker of cardiac damage and often used in the clinical diagnosis of a myocardial infarction (heart attack). When blood work is planned, patients should routinely inform their health care provider concerning supplementation of biotin at doses substantially greater than those in usual diets or in routine daily multivitamins.

Linus Pauling Institute Recommendation

Little is known regarding the amount of dietary biotin required to promote optimal health or prevent chronic disease. The Linus Pauling Institute supports the recommendation made by the National Academy of Medicine, which is 30 micrograms (μg) of biotin per day for adults. A varied diet should provide enough biotin for most people. However, following the Linus Pauling Institute recommendation to take a daily multivitamin-mineral supplement will generally provide an intake of at least 30 μg/day of biotin.

Older adults (>50 years)

Presently, there is no indication that older adults have an increased requirement for biotin. If dietary biotin intake is not sufficient, a daily multivitamin-mineral supplement will generally provide an intake of at least 30 μg of biotin per day.

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Folate

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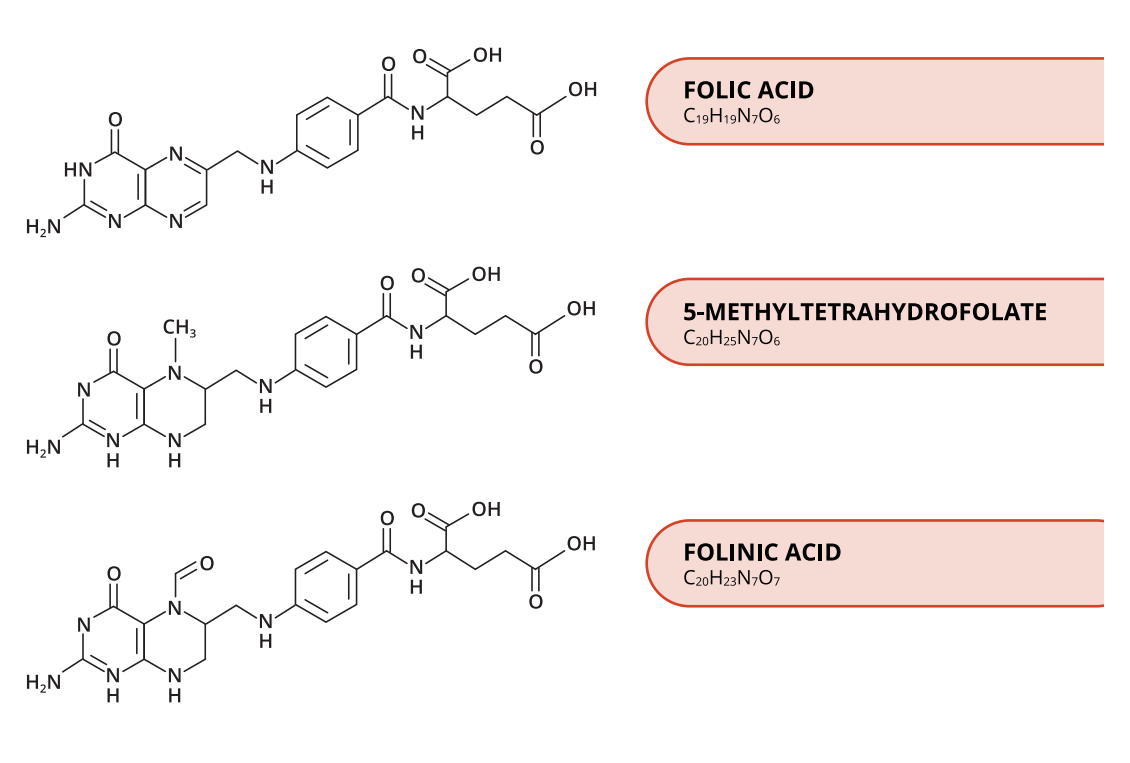
Summary

- Folate is a generic term referring to both natural folates in food and folic acid, the synthetic form used in supplements and fortified food. Folate is critical in the metabolism of nucleic acid precursors and several amino acids, as well as in methylation reactions. *(More information)*
- Severe deficiency in either folate or vitamin B_{12} can lead to megaloblastic anemia, which causes fatigue, weakness, and shortness of breath. Improper treatment of vitamin B_{12}-dependent megaloblastic anemia with high dose supplemental folic acid can potentially delay the diagnosis of vitamin B_{12} deficiency and thus leave the individual at risk of developing irreversible brain damage. *(More information)*
- Folate status is influenced by the presence of genetic variations in folate metabolism, particularly those found in the 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene. *(More information)*
- Inadequate folate status during early pregnancy increases the risk of congenital anomalies. The introduction of mandatory folic acid fortification of refined grain products in the US in 1998 has reduced the prevalence of neural tube defects (NTDs) in newborns. Yet, folate status is considered inadequate in a majority of women of childbearing age worldwide. Moreover, genetic factors might modify the risk of NTDs by increasing the susceptibility to folate deficiency during pregnancy. Several studies are currently investigating the role of folic acid supplementation in the prevention of congenital anomalies other than NTDs. *(More information)*
- Folate deficiency and elevated concentrations of homocysteine in the blood are associated with increased risk of cardiovascular disease (CVD). Although folic acid supplementation has been proven effective to control circulating homocysteine concentrations, the effect of homocysteine lowering on the incidence of CVD is still debated. *(More information)*
- Low folate status has been linked to increased cancer risk. However, intervention trials with high doses of folic acid have not generally shown any benefit on cancer incidence. *(More information)*
- Prospective cohort studies have reported an inverse association between folate status and colorectal cancer (CRC) risk, especially among men. The relationship between folate status and cancer risk is however complex and requires further research. *(More information)*
- Folate is essential for brain development and function. Low folate status and/or high homocysteine concentrations are associated with cognitive dysfunction in aging (from mild impairments to dementia). Whether supplemental B-vitamins, including folic acid, will have long-term benefits in maintaining cognitive health is not yet known. *(More information)*
- Several autosomal recessive disorders affecting folate transport and metabolism can be treated with high doses of folinic acid, a folate derivative. *(More information)*

Folate is a water-soluble B-vitamin, which is also known as vitamin B_9 or folacin. Naturally occurring folates exist in many chemical forms; folates are found in food, as well as in metabolically active forms in the human body. Folic acid is the major synthetic form found in fortified foods and vitamin supplements. Other synthetic forms include folinic acid (**Figure 1**) and levomefolic acid. Folic acid has no biological activity unless converted into folates (1). In the following discussion, forms found in food or the body are referred to as "folates," while the form found in supplements or fortified food is referred to as "folic acid."

Figure 1. Chemical Structures

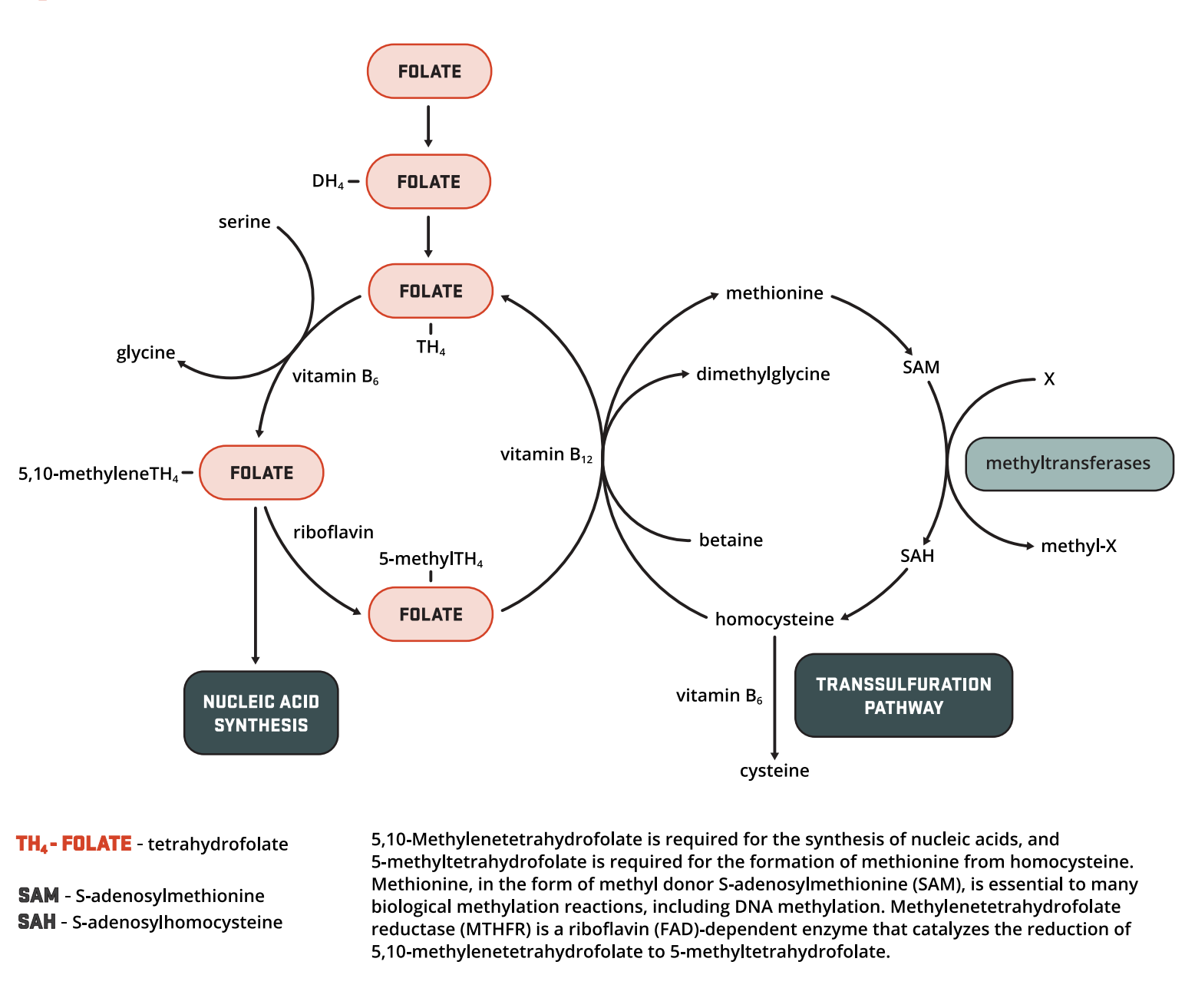


Function

One-carbon metabolism

The only function of folate coenzymes in the body appears to be in mediating the transfer of one-carbon units (2). Folate coenzymes act as acceptors and donors of one-carbon units in a variety of reactions critical to the metabolism of nucleic acids and amino acids (**Figure 2**) (3).

Figure 2. Overview of One-carbon Metabolism


FOLATE
DH₄ – FOLATE
serine
glycine
FOLATE
TH₄
vitamin B₆
5,10-methyleneTH₄ – FOLATE
riboflavin
5-methylTH₄
FOLATE
NUCLEIC ACID SYNTHESIS
vitamin B₁₂
methionine
dimethylglycine
betaine
homocysteine
SAM
X
methyltransferases
SAH
methyl-X
vitamin B₆
TRANSSULFURATION PATHWAY
cysteine
TH₄ - FOLATE - tetrahydrofolate
SAM - S-adenosylmethionine
SAH - S-adenosylhomocysteine
5,10-Methylenetetrahydrofolate is required for the synthesis of nucleic acids, and 5-methyltetrahydrofolate is required for the formation of methionine from homocysteine. Methionine, in the form of methyl donor S-adenosylmethionine (SAM), is essential to many biological methylation reactions, including DNA methylation. Methylenetetrahydrofolate reductase (MTHFR) is a riboflavin (FAD)-dependent enzyme that catalyzes the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate.

Nucleic acid metabolism

Folate coenzymes play a vital role in DNA metabolism through two different pathways. (1) The synthesis of DNA from its precursors (thymidine and purines) is dependent on folate coenzymes. (2) A folate coenzyme is required for the synthesis of methionine from homocysteine, and methionine is required for the synthesis of S-adenosylmethionine (SAM). SAM is a methyl group (one-carbon unit) donor used in most biological methylation reactions, including the methylation of a number of sites within DNA, RNA, proteins, and phospholipids. The methylation of DNA plays a role in controlling gene expression and is critical during cell differentiation. Aberrations in DNA methylation have been linked to the development of cancer (see Cancer).

Amino acid metabolism

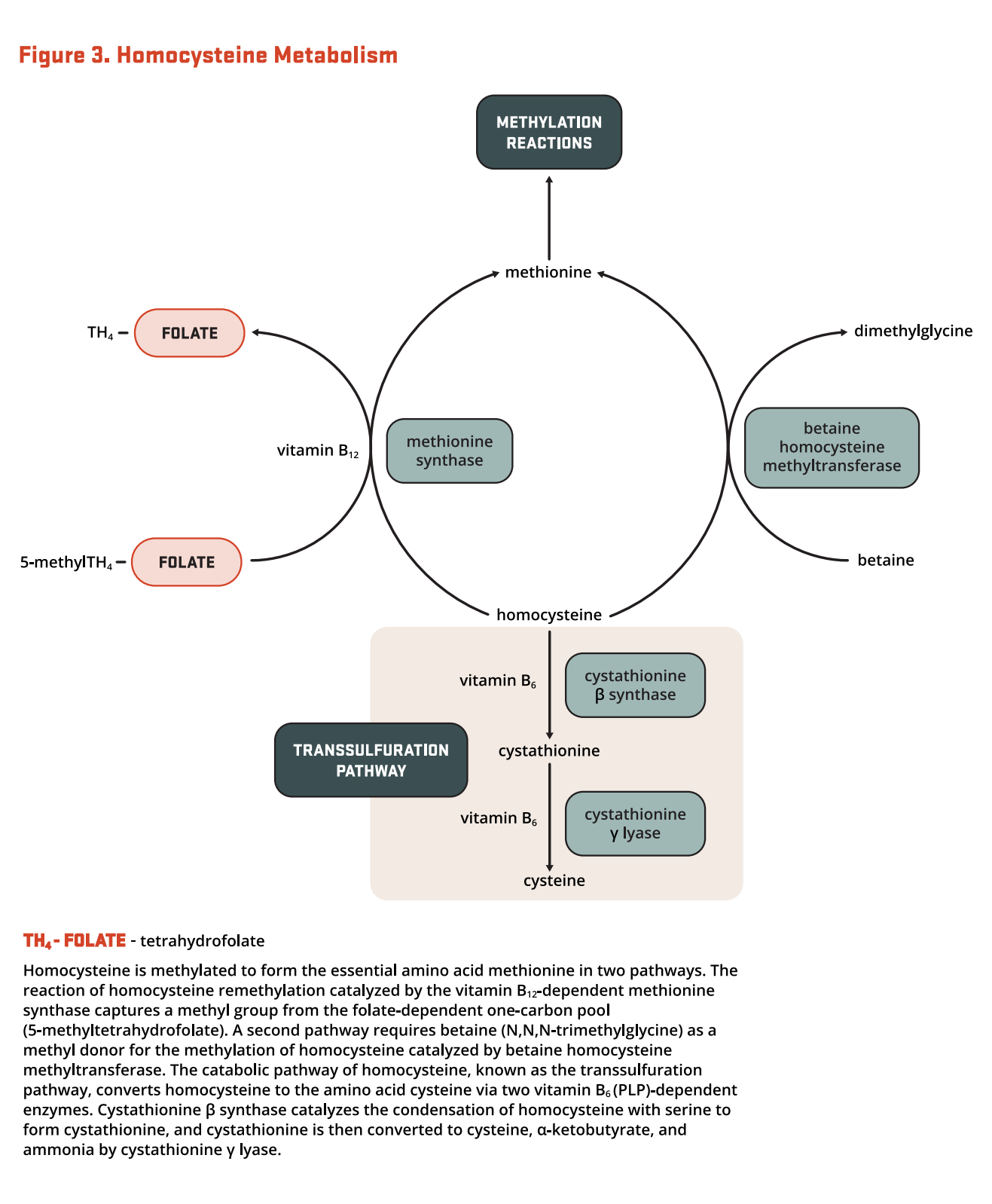
Folate coenzymes are required for the metabolism of several important amino acids, namely methionine, cysteine, serine, glycine, and histidine. The synthesis of methionine from homocysteine is catalyzed by methionine synthase, an enzyme that requires not only folate (as 5-methyltetrahydrofolate) but also vitamin B_{12}. Thus, folate (and/or vitamin B_{12}) deficiency can result in decreased synthesis of methionine and an accumulation of homocysteine. Elevated blood concentrations of homocysteine have been considered for many years to be a risk factor for some chronic diseases, including cardiovascular disease and dementia (see Disease Prevention).

Nutrient interactions

Vitamin B_{12} and vitamin B_6

The metabolism of homocysteine, an intermediate in the metabolism of sulfur-containing amino acids, provides an example of the interrelationships among nutrients necessary for optimal physiological function and health. Healthy individuals utilize two different pathways to metabolize homocysteine (**Figure 3**). One pathway (methionine synthase) synthesizes methionine from homocysteine and is dependent on both folate and vitamin B_{12} as cofactors. The other pathway converts homocysteine to another amino acid, cysteine, and requires two vitamin B_6-dependent enzymes. Thus, the concentration of homocysteine in the blood is regulated by three B-vitamins: folate, vitamin B_{12}, and vitamin B_6 (4). In some individuals, riboflavin (vitamin B_2) is also involved in the regulation of homocysteine concentrations (see the article on Riboflavin).

Figure 3. Homocysteine Metabolism


METHYLATION REACTIONS
methionine
TH₄ – FOLATE
vitamin B₁₂
methionine synthase
5-methylTH₄ – FOLATE
dimethylglycine
betaine homocysteine methyltransferase
betaine
homocysteine
vitamin B₆
cystathionine β synthase
TRANSSULFURATION PATHWAY
cystathionine
vitamin B₆
cystathionine γ lyase
cysteine
TH₄ - FOLATE - tetrahydrofolate
Homocysteine is methylated to form the essential amino acid methionine in two pathways. The reaction of homocysteine remethylation catalyzed by the vitamin B₁₂-dependent methionine synthase captures a methyl group from the folate-dependent one-carbon pool (5-methyltetrahydrofolate). A second pathway requires betaine (N,N,N-trimethylglycine) as a methyl donor for the methylation of homocysteine catalyzed by betaine homocysteine methyltransferase. The catabolic pathway of homocysteine, known as the transsulfuration pathway, converts homocysteine to the amino acid cysteine via two vitamin B₆ (PLP)-dependent enzymes. Cystathionine β synthase catalyzes the condensation of homocysteine with serine to form cystathionine, and cystathionine is then converted to cysteine, α-ketobutyrate, and ammonia by cystathionine γ lyase.

Riboflavin

Although less well recognized, folate has an important metabolic interaction with riboflavin. Riboflavin is a precursor of flavin adenine dinucleotide (FAD), a coenzyme required for the activity of the folate-metabolizing enzyme, 5,10-methylenetetrahydrofolate reductase (MTHFR). FAD-dependent MTHFR in turn catalyzes the reaction that generates 5-methyltetrahydrofolate (see **Figure 2** above). This active form of folate is required to form methionine from homocysteine. Along with other B-vitamins, higher riboflavin intakes have been associated with decreased plasma homocysteine concentrations (5). The effects of riboflavin on folate metabolism appear to be greatest in individuals homozygous for the common c.677C>T polymorphism (i.e., TT genotype) in the *MTHFR* gene (see Genetic variation in folate requirements) (6). These individuals (about 10% of adults worldwide) typically present with low folate status, along with elevated homocysteine concentrations, particularly when folate and/or riboflavin intake is suboptimal. The elevated homocysteine concentration in these individuals, however, is highly responsive to lowering with riboflavin supplementation, confirming the importance of the riboflavin-*MTHFR* interaction (7).

Vitamin C

Vitamin C may limit degradation of natural folate coenzymes and supplemental folic acid in the stomach and thus improve folate bioavailability. A cross-over trial in nine healthy men found that oral co-administration of 5-methyltetrahydrofolic acid (343 μg) and vitamin C (289 mg or 974 mg) was associated with higher concentrations of serum folate compared to 5-methyltetrahydrofolic acid alone (8). Moreover, a recent study suggested that several genetic variations of folate metabolism might influence the effect of vitamin C on folate metabolism (9).

Bioavailability

Dietary folates exist predominantly in the polyglutamyl form (containing several glutamate residues), whereas folic acid—the synthetic vitamin form—is a monoglutamate, containing just one glutamate moiety. In addition, natural folates are reduced molecules, whereas folic acid is fully oxidized. These chemical differences have major implications for the bioavailability of the vitamin such that folic acid is considerably more bioavailable than naturally occurring food folates at equivalent intake levels.

The intestinal absorption of dietary folates is a two-step process that involves the hydrolysis of folate polyglutamates to the corresponding monoglutamyl derivatives, followed by their transport into intestinal cells. There, folic acid is converted into a naturally occurring folate, namely 5-methyltetrahydrofolate, which is the major circulating form of folate in the human body (see **Figure 1** above).

The bioavailability of naturally occurring folates is inherently limited and variable. There is much variability in the ease with which folates are released from different food matrices, and the polyglutamyl "tail" is removed (de-conjugation) before uptake by intestinal cells. Also, other dietary constituents can contribute to instability of labile folates during the processes of digestion. As a result, naturally occurring folates show incomplete bioavailability compared with folic acid. The bioavailability of folic acid, in contrast, is assumed to be 100% when ingested as a supplement, while folic acid in fortified food is estimated to have about 85% the bioavailability of supplemental folic acid.

Of note, folate recommendations in the US and certain other countries are now expressed as Dietary Folate Equivalents (DFEs), a calculation that was devised to take into account the greater bioavailability of folic acid compared to naturally occurring dietary folates (see The Recommended Dietary Allowance).

Transport

Folate and its coenzymes require transporters to cross cell membranes. Folate transporters include the reduced folate carrier (RFC), the proton-coupled folate transporter (PCFT), and the folate receptor proteins, FRα and FRβ. Folate homeostasis is supported by the ubiquitous distribution of folate transporters, although abundance and importance vary among tissues (10). PCFT plays a major role in folate intestinal transport since mutations affecting the gene encoding PCFT cause hereditary folate malabsorption. Defective PCFT also leads to impaired folate transport into the brain (see Disease Treatment). FRα and RFC are also critical for folate transport across the blood-brain barrier when extracellular folate is either low or high, respectively. Folate is essential for the proper development of the embryo and the fetus. The placenta is known to concentrate folate to the fetal circulation, leading to higher folate concentrations in the fetus compared to those found in the pregnant woman. All three types of receptors have been associated with folate transport across the placenta during pregnancy (11).

Deficiency

Causes

Folate deficiency is most often caused by a dietary insufficiency; however, folate deficiency can also occur in a number of other situations. For example, chronic and heavy alcohol consumption is associated with diminished absorption of folate (in addition to low dietary intake), which can lead to folate deficiency (12). Smoking is also associated with low folate status. In one study, folate concentrations in blood were about 15% lower in smokers compared to nonsmokers (13). Additionally, impaired folate transport to the fetus has been described in pregnant women who either smoked or abused alcohol during their pregnancy (14, 15).

Pregnancy is a time when the folate requirement is greatly increased to sustain the demand for rapid cell replication and growth of fetal, placental, and maternal tissue. Conditions such as cancer or inflammation can also result in increased rates of cell division and metabolism, causing an increase in the body's demand for folate (16). Moreover, folate deficiency can result from some malabsorptive conditions, including inflammatory bowel diseases (Crohn's disease and ulcerative colitis) and celiac disease (17). Several medications may also contribute to folate deficiency (see Drug interactions). Finally, a number of genetic diseases affecting folate absorption, transport, or metabolism can cause folate deficiency or impede its metabolic functions (see Disease Treatment).

Symptoms

Clinical folate deficiency leads to megaloblastic anemia, which is reversible with folic acid treatment. Rapidly dividing cells like those derived from bone marrow are most vulnerable to the effects of folate deficiency since DNA synthesis and cell division are dependent on folate coenzymes. When folate supply to the rapidly dividing cells of the bone marrow is inadequate, blood cell division is reduced, resulting in fewer but larger red blood cells. This type of anemia is called megaloblastic or macrocytic anemia, referring to the enlarged, immature red blood cells. Neutrophils, a type of white blood cell, become hypersegmented, a change that can be found by examining a blood sample microscopically. Because normal red blood cells have a lifetime in the circulation of approximately four months, it can take months for folate-deficient individuals to develop the characteristic megaloblastic anemia. Progression of such an anemia leads to a decreased oxygen carrying capacity of the blood and may ultimately result in symptoms of fatigue, weakness, and shortness of breath (1). It is important to point out that megaloblastic anemia resulting from folate deficiency is identical to the megaloblastic anemia resulting from vitamin B_{12} deficiency, and further clinical testing is required to diagnose the true cause of megaloblastic anemia (see Toxicity).

Individuals in the early stages of folate deficiency may not show obvious symptoms, but blood concentrations of homocysteine may increase (see Disease Prevention). Yet, the concentration of circulating homocysteine is not a specific indicator of folate status, as elevated homocysteine can be the result of vitamin B_{12} and other B-vitamin deficiencies, lifestyle factors, and renal insufficiency. Subclinical deficiency is typically detected by measurement of folate concentrations in serum/plasma or in red blood cells.

The Recommended Dietary Allowance (RDA)

Determination of the RDA

Traditionally, the dietary folate requirement was defined as the amount needed to prevent a deficiency severe enough to cause symptoms like anemia. The most recent RDA (1998; **Table 1**) was based primarily on the adequacy of red blood cell folate concentrations at different levels of folate intake, as judged by the absence of abnormal hematological indicators. Red cell folate has been shown to correlate with liver folate stores and is used as an indicator of long-term folate status. Plasma folate reflects recent folate intake and is not a reliable biomarker for folate status. Maintenance of normal blood homocysteine concentrations, an indicator of one-carbon metabolism, was considered only as an ancillary indicator of adequate folate intake.

Because pregnancy is associated with a significant increase in cell division and other metabolic processes that require folate coenzymes, the RDA for pregnant women is considerably higher than for women who are not pregnant (3). However, the prevention of neural tube defects (NTDs) was not considered when setting the RDA for pregnant women. Rather, reducing the risk of NTDs was considered in a separate recommendation for women capable of becoming pregnant (see Disease Prevention), because the crucial events in the development of the neural tube occur before many women are aware that they are pregnant (18).

Dietary Folate Equivalents (DFEs)

When the Food and Nutrition Board of the US Institute of Medicine set the new dietary recommendation for folate, they introduced a new unit, the Dietary Folate Equivalent (DFE) (1). Use of the DFE reflects the higher bioavailability of synthetic folic acid found in supplements and fortified food compared to that of naturally occurring food folates (18).

- 1 microgram (μg) of food folate provides 1 μg of DFEs
- 1 μg of folic acid taken with meals or as fortified food provides 1.7 μg of DFEs
- 1 μg of folic acid (supplement) taken on an empty stomach provides 2 μg of DFEs

For example, a serving of food containing 60 μg of folate would provide 60 μg of DFEs, while a serving of pasta fortified with 60 μg of folic acid would provide 1.7 x 60 = 102 μg of DFEs due to the higher bioavailability of folic acid. A folic acid supplement of 400 μg taken on an empty stomach would provide 800 μg of DFEs. It should be noted that DFEs were determined in studies with adults and whether folic acid in infant formula is more bioavailable than folates in mother's milk has not been studied. Use of DFEs to determine a folate requirement for the infant would not be desirable.

Table 1. Recommended Dietary Allowance for Folate in Dietary Folate Equivalents (DFEs)

Life Stage	Age	Males (μg/day)	Females (μg/day)
Infants	0-6 months	65 (AI)	65 (AI)
Infants	7-12 months	80 (AI)	80 (AI)
Children	1-3 years	150	150
Children	4-8 years	200	200
Children	9-13 years	300	300
Adolescents	14-18 years	400	400
Adults	19 years and older	400	400
Pregnancy	all ages	-	600
Breast-feeding	all ages	-	500

Genetic variation in folate requirements

A common polymorphism or variation in the sequence of the gene for the enzyme, 5, 10-methylenetetrahydrofolate reductase (MTHFR), known as the *MTHFR* c.677C>T polymorphism, results in a thermolabile enzyme (19). The substitution of a cytosine (C) by a thymine (T) at nucleotide 677 in the exon 4 of *MTHFR* gene leads to an alanine-to-valine transition in the catalytic domain of the enzyme. Depending on the population, 20% to 53% of individuals may have inherited one T copy (677C/T genotype), and 3% to 32% of individuals may have inherited two T copies (677T/T genotype) for the *MTHFR* gene (20). MTHFR catalyzes the reduction of 5,10-methylenetetrahydrofolate (5,10-methylene THF) into 5-methyl tetrahydrofolate (5-MeTHF). The latter is the folate coenzyme required to form methionine from homocysteine (see **Figure 2** above). MTHFR activity is greatly diminished in heterozygous 677C/T (-30%) and homozygous 677T/T (-65%) individuals compared to those with the 677C/C genotype (21). Homozygosity for the mutation (677T/T) is linked to lower concentrations of folate in red blood cells and higher blood concentrations of homocysteine (22, 23). Improving folate nutritional status in elderly women with the T allele reduced plasma homocysteine concentration (24). An important unanswered question about folate is whether the present RDA is enough to compensate for the reduced MTHFR enzyme activity in individuals with at least one T allele, or whether those individuals have a higher folate requirement than the RDA (25).

Disease Prevention

Adverse pregnancy outcomes

Neural tube defects

Fetal growth and development are characterized by widespread cell division. Adequate folate is critical for DNA and RNA synthesis. Neural tube defects (NTDs) arise from failure of embryonic neural tube closure between the 21st and 27th days after conception, a time when many women may not even realize they are pregnant (26). NTDs include various malformations, such as lesions of the brain (e.g., anencephaly, encephalocele) or lesions of the spine (spina bifida), which are devastating and life-threatening (27). The prevalence of NTDs in the United States prior to fortification of food with folic acid was estimated to be 1 per 1,000 pregnancies (1). Results of randomized trials have demonstrated 60% to 100% reductions in NTD cases when women consumed folic acid supplements in addition to a varied diet during the periconceptional period (about one month before and at least one month after conception) (28, 29). The results of these and other studies prompted the US Public Health Service to recommend that all women capable of becoming pregnant consume 400 μg of folic acid daily to prevent NTDs. Women with a previously affected pregnancy were also advised to receive 4,000 μg (4 mg) of folic acid daily in order to reduce NTD recurrence (30). These recommendations were made to all women of childbearing age because adequate folate must be available very early in pregnancy, and because many pregnancies in the US are unplanned (31).

Despite the effectiveness of folic acid supplementation in improving folate status, it appears that globally only 30% of women who become pregnant correctly follow the recommendation, and there is some concern that young women from minority ethnic groups and lower socioeconomic backgrounds are the least likely to follow the recommendation (32-34). To decrease the incidence of NTDs, the US FDA implemented legislation in 1998 requiring the fortification of all enriched grain products with 1.4 mg of folic acid per kg of grain (see Sources). The required level of folic acid fortification in the US was initially estimated to provide 100 μg of additional folic acid in the average person's diet, though it probably provides even more due to overuse of folic acid by food manufacturers (25, 35). The National Birth Defects Prevention Network reported about a 30% decrease in the prevalence of NTDs in the US compared to the pre-fortification period, and the post-fortification prevalence of NTDs is 0.69 cases per 1,000 live births and fetal deaths (36).

Also, a genetic component in NTD etiology is evidenced by the increased risk in women with a family history of an NTD and also by variations in risk among ethnicities (37). Moreover, NTD occurrence can be attributed to specific folate-gene interactions. The *MTHFR* c.677C>T polymorphism and other genetic variations can increase the folate requirement and susceptibility for an NTD-affected pregnancy. Prior to the fortification era, a case-control study showed that both red blood cell and serum folate concentrations were significantly lower in pregnant women with the T/T and C/T variants compared to the wild-type C/C genotype (22), suggesting inadequate folate metabolism with specific maternal genotypes. A meta-analysis of 25 case-control studies, including 2,429 case mothers and 3,570 control mothers, showed a positive association between the maternal *MTHFR* c.677C>T polymorphism and NTDs (38). Another *MTHFR* variant, an A-to-C change at position 1298, has also been associated with reduced MTHFR activity and increased NTD risk (39). Individuals heterozygous for both of these *MTHFR* variants (677C/T + 1298A/C) exhibit lower plasma folate and higher homocysteine concentrations than individuals with 677C/T + 1298A/A (40). Combined genotypes with homozygosity G/G for the reduced folate carrier transporter (*RFC-1*) polymorphism (c.80A>G) could further contribute to NTD occurrence (41). The degree of NTD risk was also assessed with additional *MTHFR* polymorphisms (c.116C>T, c.1793G>A) (42), as well as with mutations affecting other enzymes of the one-carbon metabolism, including methionine synthase (*MTR* c.2756A>G) (43), methionine synthase reductase (*MTRR* c.66A>G) (44), and methylenetetrahydrofolate dehydrogenase (*MTHFD1* c.1958G>A) (45). While maternal genotype can impact pregnancy outcome, it appears that gene-gene interactions between mother and fetus influence it further. The risk of NTD was increased by certain genetic combinations, including maternal (*MTHFR* c.677C>T)-fetal (*MTHFR* c.677C>T) and maternal (*MTRR* c.66A>G)-fetal (*MTHFR* c.677C>T) interactions (43, 44, 46). Finally, vitamin B_{12} status has been associated with NTD risk modification in the presence of specific polymorphisms in one-carbon metabolism (47).

Cardiovascular malformations

Congenital anomalies of the heart are a major cause of infant mortality but also cause deaths in adulthood (48). Using data from the European Registration of Congenital Anomalies and Twins (EUROCAT) database, a case-control study, involving 596 cases and 2,359 controls, found that consumption of at least 400 μg/day of folic acid during the periconceptional period (one month before conception through eight weeks' post-conception, covering the period of embryonic heart development) was associated with an 18% reduced risk of congenital heart defects (49). Recent meta-analyses of 20 to 25 case-control and family-based studies observed positive associations between maternal, fetal, or paternal *MTHFR* c.677C>T variant and incidence of congenital heart defects (50, 51). Additional studies are needed to elucidate the effects of gene-nutrient interactions on the risk of congenital heart defects; however, the currently available research indicates that adequate folate intake may play an important role.

Orofacial clefts

Maternal folate status during pregnancy may influence the risk of congenital anomalies called orofacial clefts, namely cleft lip with or without cleft palate (CL/P) (52). A population-based case-control study in Norway investigated the impact of folic acid supplements in mothers of 377 newborns with CL/P, 196 with cleft palate only (CPO) and 763 controls (53). Although dietary intakes or supplements (during the first three months of pregnancy) on their own did not significantly modify the risk of CL/P, the study reported a 64% lower risk among women taking multivitamin and folic acid (≥400 μg daily) supplements in addition to dietary folates. In the same population, polymorphisms in the cystathionine β-synthase (*CBS*) gene (c.699C>T) or *MTHFR* gene (c.677C>T; when folate intake was below 400 μg/day) appeared protective, while other gene variants in the folate/one-carbon metabolism could not be linked to CL/P (54, 55). However, a recent meta-analysis of 18 studies showed an elevation of CL/P risk with the maternal 677T/T homozygosity (56). Additional studies are needed to evaluate the risk of CL/P while integrating both genetic polymorphism and folate intake parameters. Epidemiological evidence supporting a role for folate in the risk of CPO is lacking.

Other adverse pregnancy outcomes

Low birth weight has been associated with increased risk of mortality during the first year of life and may also influence health outcomes during adulthood (57). A recent systematic review and meta-analysis of eight randomized controlled trials found a positive association between folic acid supplementation and birth weight; no association with length of gestation was observed (58). Additionally, a prospective cohort study of 306 pregnant adolescents associated low folate intakes and maternal folate status during the third trimester of pregnancy with higher incidence of small for gestational age births (birth weight <10th percentile) (59). Moreover, the maternal c.677C>T *MTHFR* genotype and increased homocysteine concentrations, considered an indicator of functional folate deficiency, have been linked to lower birth weights (60).

Elevated blood homocysteine concentrations have also been associated with increased incidence of miscarriage and other pregnancy complications, including preeclampsia and placental abruption (61). A large retrospective study showed that plasma homocysteine in Norwegian women was strongly related to adverse outcomes and complications, including preeclampsia, premature delivery, and very low birth weight, in previous pregnancies (62). A recent meta-analysis of 51 prospective cohort studies linked the c.677C>T *MTHFR* variant with increased risk of preeclampsia in Caucasian and East Asian populations, reinforcing the notion that folate metabolism may play a role in the condition (63). A large multicenter, randomized, controlled trial, the Folic Acid Clinical Trial (FACT), has been initiated to evaluate whether the daily supplementation of up to 5.1 mg of folic acid throughout pregnancy could prevent preeclampsia and other adverse outcomes (e.g., maternal death, placental abruption, preterm delivery) in high-risk women (64). Adequate folate intake during pregnancy protects against megaloblastic anemia (65). A recent case-control study found a reduction in risk of autism spectrum disorders with daily folic acid consumption of 600 μg or more before and during pregnancy when mother and child carried the c.677C>T *MTHFR* genotype (66).

Thus, it is reasonable to maintain folic acid supplementation throughout pregnancy, even after closure of the neural tube, in order to decrease the risk of other problems during pregnancy. Moreover, recent systematic reviews of observational studies found no evidence of an association between folate exposure during pregnancy and adverse health outcomes in offspring, in particular childhood asthma and allergies (67, 68).

Cardiovascular disease

Homocysteine and cardiovascular disease

The results of more than 80 studies indicate that even moderately elevated concentrations of homocysteine in the blood increase the risk of cardiovascular disease (CVD) (4). Possible predispositions to vascular accidents have also been linked to genetic deficiencies in homocysteine metabolism in certain populations (69). The mechanism by which homocysteine may increase the risk of vascular disease has been the subject of a great deal of research, but it may involve adverse effects of homocysteine on blood clotting, arterial vasodilation, and thickening of arterial walls (70). Although increased homocysteine concentrations in the blood have been consistently associated with increased risk of CVD, it is unclear whether lowering circulating homocysteine will reduce CVD risk (see Folate and homocysteine). Research had initially predicted that a prolonged decrease in serum homocysteine level of 3 micromoles/liter would lower the risk of CVD by up to 25% and be a reasonable treatment goal for individuals at high risk (71, 72). However, the analysis of recent clinical trials of B-vitamin supplementation has shown that lowering homocysteine concentrations did not prevent the occurrence of a second cardiovascular event in patients with existing CVD (73, 74). Consequently, the American Heart Association recommends screening for elevated total homocysteine concentrations only in "high risk" individuals, for example, in those with personal or family history of premature cardiovascular disease, malnutrition or malabsorption syndromes, hypothyroidism, kidney failure, lupus, or individuals taking certain medications (nicotinic acid, theophylline, bile acid-binding resins, methotrexate, and L-dopa).

Folate and homocysteine

Folate-rich diets have been associated with decreased risk of CVD, including coronary artery disease, myocardial infarction (heart attack), and stroke. A study that followed 1,980 Finnish men for 10 years found that those who consumed the most dietary folate had a 55% lower risk of an acute coronary event when compared to those who consumed the least dietary folate (75). Of the three B-vitamins that regulate homocysteine concentrations, folic acid has been shown to have the greatest effect in lowering basal concentrations of homocysteine in the blood when there is no coexisting deficiency of vitamin B_{12} or vitamin B_6 (see Nutrient interactions) (76). Increasing folate intake through folate-rich food or supplements has been found to reduce homocysteine concentrations (77). Besides, blood homocysteine concentrations have declined since the FDA mandated folic acid fortification of the grain supply in the US (25). A meta-analysis of 25 randomized controlled trials, including almost 3,000 subjects, found that folic acid supplementation with 800 μg/day or more could achieve a maximal 25% reduction in plasma homocysteine concentrations. In this meta-analysis, daily doses of 200 μg and 400 μg of folic acid were associated with a 13% and 20% reduction in plasma homocysteine, respectively (78). A supplement regimen of 400 μg of folic acid, 2 mg of vitamin B_6, and 6 μg of vitamin B_{12} has been advocated by the American Heart Association if an initial trial of a folate-rich diet (see Sources) is not successful in adequately lowering homocysteine concentrations (79).

Several polymorphisms in folate/one-carbon metabolism modify homocysteine concentrations in blood (80). In particular, the effect of the c.677C>T *MTHFR* variant has been examined in relation to folic acid fortification policies worldwide. The analysis of randomized trials, including 59,995 subjects without a history of CVD, revealed that the difference in homocysteine concentrations between T/T and C/C genotypes was greater in low-folate regions compared to regions with food fortification policy (3.12 vs. 0.13 micromoles/liter) (81). Although folic acid supplementation effectively decreases homocysteine concentrations, it is not yet clear whether it also decreases risk for CVD. A recent meta-analysis of 19 randomized clinical trials, including 47,921 subjects with preexisting cardiovascular or renal disease, found that homocysteine lowering through folic acid and other B-vitamin supplementation failed to reduce the incidence of CVD despite significant reductions in plasma homocysteine concentrations (74). Other meta-analyses have confirmed the lack of causality between the lowering of homocysteine and the risk of CVD (80-82), including the risk of stroke (83, 84). Consequently, the American Heart Association removed its recommendation for using folic acid to prevent cardiovascular disease in high-risk women (85). It should be noted that the majority of prevention trials to date have been performed in CVD patients with advanced disease. The evidence supporting a beneficial role for folate and related B-vitamins appears to be strongest for the primary prevention of stroke (86). The introduction of mandatory folic acid fortification has been associated with a decline in stroke-related mortality in North America, adding further support to the potential benefit of enhancing folate status and/or lowering homocysteine in the prevention of stroke (87).

Despite the controversy regarding the role of homocysteine lowering in CVD prevention, some studies have investigated the effect of folic acid supplementation on the development of atherosclerosis, a known risk factor for vascular accidents. The measurement of the carotid intima-media thickness (CIMT) is a surrogate endpoint for early atherosclerosis and a predictor for cardiovascular events (88). The meta-analysis of 10 randomized trials testing the effect of folic acid supplementation showed a significant reduction in CIMT in subjects with chronic kidney diseases and in those at risk for CVD, but not in healthy participants (89). Endothelial dysfunction is a common feature in atherosclerosis and vascular disease. High doses of folic acid (400-10,000 μg/day) have been associated with improvements in vascular health in both healthy and CVD subjects (90). Although recent trials failed to demonstrate any cardiovascular protection from folic acid supplementation, low folate intake is a known risk factor for vascular disease, and more research is needed to explore the role of folate in maintaining vascular health (91).

Cancer

Cancer is thought to arise from DNA damage in excess of ongoing DNA repair and/or the inappropriate expression of critical genes. Because of the important roles played by folate in DNA and RNA synthesis and methylation, it is possible that inadequate folate intake contributes to genome instability and chromosome breakage that often characterize cancer development. In particular, DNA replication and repair are critical for genome maintenance, and the shortage in nucleotides caused by folate deficiency might lead to genome instability and DNA mutations. A decrease in 5,10-methylene THF can compromise the conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP) by the enzyme thymidylate synthase (TS), causing uracil accumulation and thymine depletion. This could then lead to uracil misincorporation into DNA during replication or repair, and cause DNA damage, including point mutations and strand breaks (92). Since 5,10-methylene THF is also the MTHFR enzyme substrate, it is plausible that a reduction of MTHFR activity with the c.677C>T polymorphism may increase the use of 5,10-methylene THF for thymidylate synthesis and prevent DNA damage. However, this hypothesis might only be valid in a situation of folate deficiency (93). Conversely, it was argued that folic acid supplementation could fuel DNA synthesis, therefore promoting tumor growth. This is supported by the observation that TS can function like a tumor promoter (oncogene), while a reduction in TS activity is linked to a lower risk of cancer (94, 95). Additionally, antifolate molecules that block the thymidylate synthesis pathway are successfully used in cancer therapy (96). Folate also controls the homocysteine/methionine cycle and the pool of S-adenosylmethionine (SAM), the methyl donor for methylation reactions. Thus, folate deficiency may impair DNA and protein methylation and alter the expression of genes involved in DNA repair, proliferation and cell death. Global DNA hypomethylation, a typical hallmark of cancer, causes genome instability and chromosome breaks (reviewed in 97).

The consumption of at least five servings of fruit and vegetables daily has been consistently associated with a decreased incidence of cancer (98). Fruit and vegetables are excellent sources of folate, which may play a role in their anti-carcinogenic effect. Observational studies have found diminished folate status to be associated with site-specific cancers. While food fortification is mandatory in the US (since 1998; see Sources), concerns about the impact of high folic acid intakes on health have delayed the practice in several other countries (99). However, the most recent meta-analyses of folic acid intervention trials (supplemental doses ranging from 500 to 5,000 μg/day for at least one year) did not show any specific benefit or harm regarding total and site-specific cancer incidence (100, 101).

Colorectal cancer

A pooled analysis of 13 prospective cohort studies, which followed a total of 725,134 individuals for a 7 to 20-year period, revealed a modest, inverse association between dietary and total (from food and supplements) folate intake and colon cancer risk. Specifically, a 2% decrease in colon cancer risk was estimated for every 100 μg/day increase in total folate intake (102). A large US prospective study, which followed 525,488 subjects, ages 50 to 71 years between 1995 and 2006, correlated dietary folate, supplemental folic acid, and total folate intakes with a decreased colorectal cancer (CRC) risk (103). However, when stratified by gender, there was no association between dietary folate intake and CRC risk in women (103, 104). A lack of association between CRC risk and dietary, supplemental, and total folate intakes was also reported in another prospective study that followed more than 90,000 US postmenopausal women during an 11-year period encompassing pre- and post-fortification periods (105). These data suggest the possible influence of gender over CRC risk modification by folate. In the latter study, a significant but transient risk elevation was also observed during the post-fortification era; however, some have asserted that this is unlikely to be caused by increased folate intake due to mandatory fortification (106). Finally, a meta-analysis of 18 case-control studies found a slight reduction in CRC risk with folate from food (107). However, it is important to note that the case-control studies were highly heterogeneous, and that the authors stated that dietary fiber, vitamins, and alcohol intake could have confounded their results. Moreover, the lower limit of the highest quantile of folate intake was highly variable, ranging from 270 to 1,367 μg/day (107).

While most epidemiological research shows a protective effect of folate against colorectal cancer development, it has been suggested that high doses of supplemental folic acid may actually accelerate tumor growth in cancer patients (108). Whereas higher folate status within the normal dietary range is widely considered to be protective against cancer, some investigators remain concerned that exposure to excessively high folic acid intakes may increase the growth of pre-existing neoplasms (108). Several clinical trials addressed the effect of folic acid supplementation in patients with a history of colorectal adenoma, with trials finding a risk reduction or no effect of supplemental folic acid (109-112). A recent meta-analysis of three large randomized controlled trials in high-risk subjects did not demonstrate any increase in colorectal adenoma recurrence in subjects supplemented with 500 or 1,000 μg/day of folic acid for 24 to 42 months when compared with placebo treatment (113).

As suggested earlier, the *MTHFR* 677T/T genotype might prevent uracil misincorporation and protect DNA integrity and stability under low-folate conditions. A meta-analysis of 62 case-control and two cohort studies revealed that while the T/T variant reduces CRC risk by 12% compared to both C/T and C/C genotypes, the risk was decreased by 30% with high (348-1,583 μg/day) versus low total folate intakes (264-450 μg/day), irrespective of the genotype (114). A common polymorphism (c.2756A>G) in the *MTR* gene, which codes for methionine synthase, was also examined in relation with the risk of colorectal adenoma and cancer. Methionine synthase catalyzes the simultaneous conversion of homocysteine and 5-methylene THF into methionine and TFH, respectively. The recent meta-analysis of 27 case-control studies showed no association between *MTR* variant and cancer risk (115).

Although alcohol consumption interferes with the absorption and metabolism of folate (16), one case-control and five prospective cohort studies have reported either reduction in CRC risk among nondrinkers compared to drinkers or a lack of association (107). However, in a large prospective study that followed more than 28,000 male health professionals for 22 years, intake of more than two alcoholic drinks (>30 grams of alcohol) per day augmented CRC risk by 42% during the pre-fortification period. CRC risk was not increased during the post-fortification period, suggesting that it is the combination of high alcohol and low folate intake that might increase CRC risk. Yet, another prospective study that followed more than 69,000 female nurses for 28 years did not report a significant increase in CRC risk with alcohol intake before and after the mandatory folic acid fortification (116). In some studies, individuals who are homozygous for the c.677C>T *MTHFR* polymorphism (T/T) have been found to be at decreased risk for colon cancer when folate intake is adequate. However, when folate intake is low and/or alcohol intake is high, individuals with the (T/T) genotype have been found to be at increased risk of colorectal cancer (117, 118).

Breast cancer

Several prospective cohort and case-control studies investigating whether folate intake affects breast cancer risk have reported mixed results (119). A meta-analysis of 15 prospective studies and one nested case-control study found no relationship with dietary folate intake (120). Moderate alcohol intake has been associated with increased risk of breast cancer in women (121). The results of three prospective studies suggested that increased folate intake may reduce the risk of breast cancer in women who regularly consume alcohol (122-124). Thus, high folate intake might be associated with a risk reduction only in women whose breast cancer risk is raised by alcohol consumption. A very large prospective study in more than 88,000 nurses reported that folic acid intake was not associated with breast cancer in women who consumed less than one alcoholic drink per day. However, in women consuming at least one alcoholic drink per day, folic acid intake of at least 600 μg daily resulted in about half the risk of breast cancer compared with women who consumed less than 300 μg of folic acid daily (124). Nevertheless, whether and how alcohol consumption increases breast cancer risk is still subject to discussion (125, 126). Finally, recent meta-analyses evaluating the influence of polymorphisms in one-carbon metabolism on cancer risk found that specific variants in the gene encoding thymidylate synthase increased the risk of breast cancer in certain ethnic populations (127, 128).

Childhood cancers

The incidence of Wilms' tumors (kidney cancer) and certain types of brain cancers (neuroblastoma, ganglioneuroblastoma, and ependymoma) in children has decreased since the mandatory fortification of the US grain supply in 1998 (129). However, incidence rates were unchanged between the pre- and post-fortification periods for leukemia—a predominant childhood malignancy. Despite earlier studies linking maternal folic acid supplementation during pregnancy with the reduced risk of childhood leukemia, more recent investigations have found little evidence to support a preventive effect of folic acid (130). Several meta-analyses have also found little to no protective effect with *MTHFR* polymorphisms; however, the most recent meta-analysis of 22 case-control studies found a reduction in the risk of acute lymphoblastic leukemia (ALL) with the c.677C>T variant in Caucasians and Asians (131).

Alzheimer's disease and cognitive impairment

Alzheimer's disease (AD) is the most common form of dementia, affecting more than 5 million individuals over 65 years old in the US (132). β-amyloid plaque deposition, Tau protein-forming tangles, and increased cell death in the brain of AD patients have been associated with cognitive decline and memory loss. One study associated increased consumption of fruit and vegetables, which are abundant sources of folate, with a reduced risk of developing dementia and AD in women (133). Through its role in nucleic acid synthesis and methyl donor provision for methylation reactions, folate is critical for normal brain development and function, not only during pregnancy and after birth, but also later in life (134). In one cross-sectional study of elderly women, AD patients had significantly higher homocysteine and lower red blood cell folate concentrations compared to healthy individuals. However, there was no difference in the level of serum folate between groups, suggesting that long-term folate status, rather than recent folate intake, may be associated with the risk of AD (135).

Several investigators have described associations between increased homocysteine concentrations and cognitive impairment in the elderly (136), but prospective cohort studies have not found higher folate intakes to be associated with improved cognition (137, 138). Higher homocysteine concentrations were found in individuals suffering from dementia, including AD and vascular dementia, compared to healthy subjects (139, 140). Although deficiencies in folate, vitamin B_{12}, and vitamin B_6 could increase homocysteine concentrations, a reduction in vitamin concentrations in the serum of AD patients compared to healthy individuals could not be attributed to decreased vitamin intakes (141). It is not presently clear whether serum homocysteine is a risk factor for developing dementia or simply associated with the cognitive decline. In the last decade, a number of clinical trials have tested the use of B-vitamins to lower homocysteine and prevent or delay cognitive decline. A meta-analysis of nine randomized, placebo-controlled trials of folic acid supplementation (0.2 to 15 mg/day for a median duration of six months) in healthy individuals over 45 years of age failed to find a short-term effect on cognitive functions, including memory, speed, language, and executive functions (142). More recently, a meta-analysis of 19 randomized, placebo-controlled trials of B-vitamin supplementation found no difference in cognitive parameters between the treatment and placebo groups, despite the treatment effectively lowering homocysteine concentrations (143). Inconsistent findings across trials may be due to differences in design and methodology (reviewed in 144).

Nevertheless, a two-year randomized, placebo-controlled trial in 168 elderly subjects with mild cognitive impairment recently described the benefits of a daily regimen of 800 μg of folic acid, 500 μg of vitamin B_{12}, and 20 mg of vitamin B_6 (145, 146). Atrophy of specific brain regions affected by AD was observed in individuals of both groups, and this atrophy correlated with cognitive decline; however, the B-vitamin treatment group experienced a smaller loss of gray matter compared to the placebo group (0.5% vs. 3.7%). A greater benefit was seen in subjects with higher baseline homocysteine concentrations, suggesting the importance of lowering circulating homocysteine in prevention of cognitive decline and dementia. Although encouraging, the effect of B-vitamin supplementation needs to be further studied in larger trials that evaluate long-term outcomes, such as the incidence of AD.

Disease Treatment

Metabolic diseases

Folinic acid (see **Figure 1** above), a tetrahydrofolic acid derivative, is used in the clinical management of rare inborn errors that affect folate transport or metabolism (reviewed in 147). Such conditions are of autosomal recessive inheritance, meaning only individuals receiving two copies of the mutated gene (one from each parent) develop the disease.

Hereditary folate malabsorption

Hereditary folate malabsorption is caused by mutations in the *SLC46A1* gene coding for the folate transporter PCFT and typically affects gastrointestinal folate absorption and folate transport into the brain (148). Patients present with low to undetectable concentrations of folate in serum and cerebrospinal fluid, pancytopenia (low number of all blood cells), impaired immune responses that increase susceptibility to infections, and a general failure to thrive (149). Neurologic symptoms, including seizures, have also been observed (150). Clinical improvements have been recorded following parenteral provision of folinic acid (151).

Cerebral Folate Deficiency (CFD) syndrome

CFD is characterized by low levels of folate coenzymes in cerebrospinal fluid despite normal concentrations of folate in blood. Folate transport across the blood-brain barrier is compromised in CFD and has been linked either to the presence of antibodies blocking the folate receptor FRα or to mutations in the *FOLR1* gene encoding FRα (152, 153). Neurologic abnormalities, along with visual and hearing impairments, have been described in children with CFD; autism spectrum disorder (ASD) is present in some cases. Folinic acid (also known as leucovorin) can enter the brain and normalize the level of folate coenzymes and has been shown to normalize folate concentrations and improve various social interactions in CFD, including mood, behavior, and verbal communication in children with ASD (152, 154, 155).

Dihydrofolate reductase (DHFR) deficiency

DHFR is the NADPH-dependent enzyme that catalyzes the reduction of dihydrofolic acid (DHF) to tetrahydrofolic acid (THF). DHFR is also required to convert folic acid to DHF. DHFR deficiency is characterized by megaloblastic anemia and cerebral folate deficiency causing intractable seizures and mental deficits. Although folinic acid treatment can alleviate the symptoms of DHFR deficiency, early diagnosis is essential to prevent irreversible brain damage and improve clinical outcomes (156, 157).

Sources

Food sources

Green leafy vegetables (foliage) are rich sources of folate and provide the basis for its name. Citrus fruit juices, legumes, and fortified foods are also excellent sources of folate (1); the folate content of fortified cereal varies greatly. A number of folate-rich foods are listed in **Table 2**, along with their folate content in micrograms (μg). For more information on the nutrient content of specific foods, search USDA's FoodData Central.

Table 2. Some Food Sources of Folate and Folic Acid

Food	Serving	Folate (μg DFEs)
Lentils (mature seeds, cooked, boiled)	½ cup	179
Garbanzo beans (chickpeas, cooked, boiled)	½ cup	141
Asparagus (cooked, boiled)	½ cup (~6 spears)	134
Spinach (cooked, boiled)	½ cup	131
Lima beans (large, mature seeds, cooked, boiled)	½ cup	78
Orange juice (raw)	6 fl. oz.	56
Spaghetti (enriched, cooked)	1 cup	167*
White rice (enriched, cooked)	1 cup	153*
Bread (enriched)	1 slice	84*

*To help prevent neural tube defects, the US FDA required the addition of 1.4 milligrams (mg) of folic acid per kilogram (kg) of grain to be added to refined grain products, which are already enriched with niacin, thiamin, riboflavin, and iron, as of January 1, 1998. The addition of nutrients to food in order to prevent a nutritional deficiency or restore nutrients lost in processing is known as fortification. The FDA initially estimated that this level of fortification would increase dietary intake by an average of 100 μg folic acid/day (26). However, further evaluations based on observational studies suggested increases twice that predicted by the FDA (35). The prevalence of low folate concentrations in both serum and red blood cells is currently below 1% in the US population, compared to 24% and 3.5%, respectively, before the fortification period (158).

Supplements

The principal form of supplementary folate is folic acid. It is available in single-ingredient and combination products, such as B-complex vitamins and multivitamins. Doses of 1 mg or greater require a prescription (159). Additionally, folinic acid, a tetrahydrofolic acid derivative, is used to manage certain metabolic diseases (see Disease Treatment). Further, the US FDA has approved the supplementation of folate in oral contraceptives. The addition of levomefolate calcium (the calcium salt of MeTHF; 451 μg/tablet) to oral contraceptives is intended to raise folate status in women of childbearing age (160). According to a US national survey, only 24% of non-pregnant women aged 15-44 years are meeting the current recommendation of 400 μg/day of folic acid (161).

Safety

Toxicity

No adverse effects have been associated with the consumption of excess folate from food. Concerns regarding safety are limited to synthetic folic acid intake. Deficiency of vitamin B_{12}, though often undiagnosed, may affect a significant number of people, especially older adults (see the article on Vitamin B_{12}). One symptom of vitamin B_{12} deficiency is megaloblastic anemia, which is indistinguishable from that associated with folate deficiency (see Deficiency). Large doses of folic acid given to an individual with an undiagnosed vitamin B_{12} deficiency could correct megaloblastic anemia without correcting the underlying vitamin B_{12} deficiency, leaving the individual at risk of developing irreversible neurologic damage. Such cases of neurologic progression in vitamin B_{12} deficiency have been mostly seen at folic acid doses of 5,000 μg (5 mg) and above. In order to be very sure of preventing irreversible neurological damage in vitamin B_{12}-deficient individuals, the Food and Nutrition Board of the US Institute of Medicine advises that all adults limit their intake of folic acid (supplements and fortification) to 1,000 μg (1 mg) daily (**Table 3**). The Board also noted that vitamin B_{12} deficiency is very rare in women in their childbearing years, making the consumption of folic acid at or above 1,000 μg/day unlikely to cause problems (1); however, there are limited data on the effects of large doses.

Table 3. Tolerable Upper Intake Level (UL) for Folic Acid

Age Group	UL (μg/day)
Infants 0-12 months	Not possible to establish*
Children 1-3 years	300
Children 4-8 years	400
Children 9-13 years	600
Adolescents 14-18 years	800
Adults 19 years and older	1,000

*Source of intake should be from food and formula only.

The saturation of DHFR metabolic capacity by oral doses of folic acid has been associated with the appearance of unmetabolized folic acid in blood (162). Hematologic abnormalities and poorer cognition have been associated with the presence of unmetabolized folic acid in vitamin B_{12}-deficient older adults (≥60 years) (163, 164). A small study conducted in postmenopausal women also raised concerns about the effect of exposure to unmetabolized folic acid on immune function (165). In a small, randomized, open-label trial in 38 women of reproductive age receiving 30 weeks of daily multivitamin supplements, daily supplementation with either 1.1 mg or 5 mg of folic acid resulted in the transient appearance of unmetabolized folic acid in blood over the first 12 weeks of supplementation (166). However, unmetabolized folic acid concentrations returned to baseline levels at the end of the study, suggesting that adaptive mechanisms eventually converted folic acid to reduced forms of folate. Nonetheless, the use of supplemental levomefolate (5-methyl THF) may provide an alternative to prevent the potential negative effects of unconverted folic acid in older adults.

Drug interactions

When nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin or ibuprofen, are taken in very large therapeutic dosages (i.e., to treat severe arthritis), they may interfere with folate metabolism. In contrast, routine use of NSAIDs has not been found to adversely affect folate status. The anticonvulsant, phenytoin, has been shown to inhibit the intestinal absorption of folate, and several studies have associated decreased folate status with long-term use of the anticonvulsants, phenytoin, phenobarbital, and primidone (167). However, few studies controlled for differences in dietary folate intake between anticonvulsant users and nonusers. Also, taking folic acid at the same time as the cholesterol-lowering agents, cholestyramine and colestipol, may decrease the absorption of folic acid (159). Methotrexate is a folate antagonist used to treat a number of diseases, including cancer, rheumatoid arthritis, and psoriasis. Some of the side effects of methotrexate are similar to those of severe folate deficiency, and supplementation with folic or folinic acid is used to reduce antifolate toxicity. Other antifolate molecules currently used in cancer therapy include aminopterin, pemetrexed, pralatrexate, and raltitrexed (96). Further, a number of other medications have been shown to have antifolate activity, including trimethoprim (an antibiotic), pyrimethamine (an antimalarial), triamterene (a blood pressure medication), and sulfasalazine (a treatment for ulcerative colitis). Early studies of oral contraceptives (birth control pills) containing high doses of estrogen indicated adverse effects on folate status; however, this finding has not been supported in more recent studies that used low-dose oral contraceptives and controlled for dietary folate (168).

Linus Pauling Institute Recommendation

The available scientific evidence shows that adequate folate intake prevents neural tube defects and other poor outcomes of pregnancy; is helpful in lowering the risk of some forms of cancer, especially in genetically susceptible individuals; and may lower the risk of cardiovascular disease. The Linus Pauling Institute recommends that adults take a daily multivitamin/mineral supplement, which typically contains 400 μg of folic acid, the Daily Value (DV). Even with a larger than average intake of folic acid from fortified food, it is unlikely that an individual's daily folic acid intake would regularly exceed the tolerable upper intake level of 1,000 μg/day established by the Institute of Medicine (see Safety).

Older adults (>50 years)

The recommendation for 400 μg/day of supplemental folic acid as part of a daily multivitamin/mineral supplement, in addition to a folate-rich diet, is especially important for older adults because blood homocysteine concentrations tend to increase with age (see Disease Prevention).

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Niacin

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Español

Summary

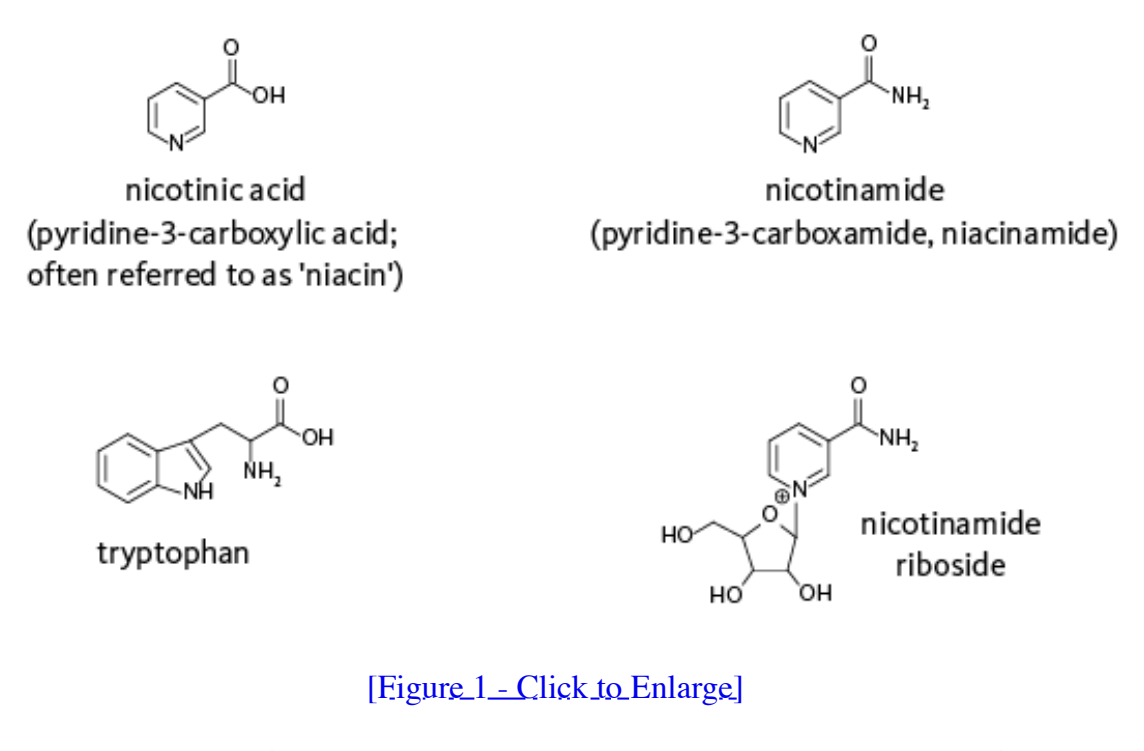
- Dietary precursors of nicotinamide adenine dinucleotide (NAD), including nicotinic acid, nicotinamide, and nicotinamide riboside, are collectively referred to as niacin or vitamin B$_3$. The essential amino acid tryptophan can also be converted into NAD via the kynurenine pathway. *(More information)*
- NAD can be phosphorylated (NADP) and reduced (NADH and NADPH). NAD functions in oxidation-reduction (redox) reactions and non-redox reactions. *(More information)*
- Pellagra is the disease of severe niacin deficiency. It is characterized by symptoms affecting the skin, the digestive system, and the nervous system; pellagra can lead to death if left untreated. *(More information)*
- Causes of niacin deficiency include inadequate oral intake, poor bioavailability from unlimed grains, defective tryptophan absorption, metabolic disorders, and the long-term use of chemotherapeutic treatments. *(More information)*
- Dietary intake requirements for niacin are based on the urinary excretion of niacin metabolites. *(More information)*
- NAD is the sole substrate for PARP enzymes and sirtuins involved in DNA repair activities; thus, NAD is critical for genome stability. Several studies, mostly using *in vitro* and animal models, suggest a possible role for niacin in cancer prevention. In a recent phase III trial, a daily pharmacologic dose of nicotinamide was found to reduce the rate of premalignant skin lesions and nonmelanoma cancers in high-risk subjects. *(More information)*
- Despite promising initial results, nicotinamide administration has failed to prevent or delay the onset of type 1 diabetes mellitus in high-risk relatives of type 1 diabetic patients. Future research might explore the use of nicotinamide in combined therapy and evaluate activators of NAD-dependent enzymes. *(More information)*
- At pharmacologic doses, nicotinic acid improved lipid profiles of patients with a history of vascular disease yet failed to reduce recurrent cardiovascular events or mortality. *(More information)*
- Elevated tryptophan breakdown in the kynurenine pathway and niacin deficiency have been reported in HIV-positive people. However, at present, a better understanding of the role of kynurenine pathway and other NAD biosynthetic pathways during HIV infection is needed to establish whether this population could benefit from niacin supplementation. *(More information)*
- Most adverse effects of niacin (nicotinic acid and nicotinamide) have been reported with pharmacological doses of nicotinic acid. The tolerable upper intake level (UL) for niacin is based on preventing skin flushing, nicotinic acid's most prominent side effect. The co-administration of laropiprant — a prostaglandin D2 receptor-1 antagonist — helps reduce nicotinic acid-induced skin flushing. *(More information)*

Niacin or vitamin B$_3$ is a water-soluble vitamin used by the body to form the nicotinamide coenzyme, NAD$^+$. The term 'niacin' is often used to refer to nicotinic acid (pyridine-3-carboxylic acid) only, although other vitamers with a pyridine ring, including nicotinamide (pyridine-3-carboxamide) and nicotinamide riboside, also contribute to NAD$^+$ formation (1). None of the vitamers are related to the nicotine found in tobacco, although their names are similar. Likewise, nicotine — but not nicotinic acid — is an agonist of the nicotinic receptors that respond to the neurotransmitter, acetylcholine.

Metabolism

Essential to all forms of life, the nicotinamide coenzyme NAD$^+$ is synthesized in the body from four precursors that are provided in the diet: nicotinic acid, nicotinamide, nicotinamide riboside, and tryptophan (**Figure 1**).

Figure 1. Precursors of Nicotinamide Adenine Dinucleotide (NAD$^+$) in the Diet

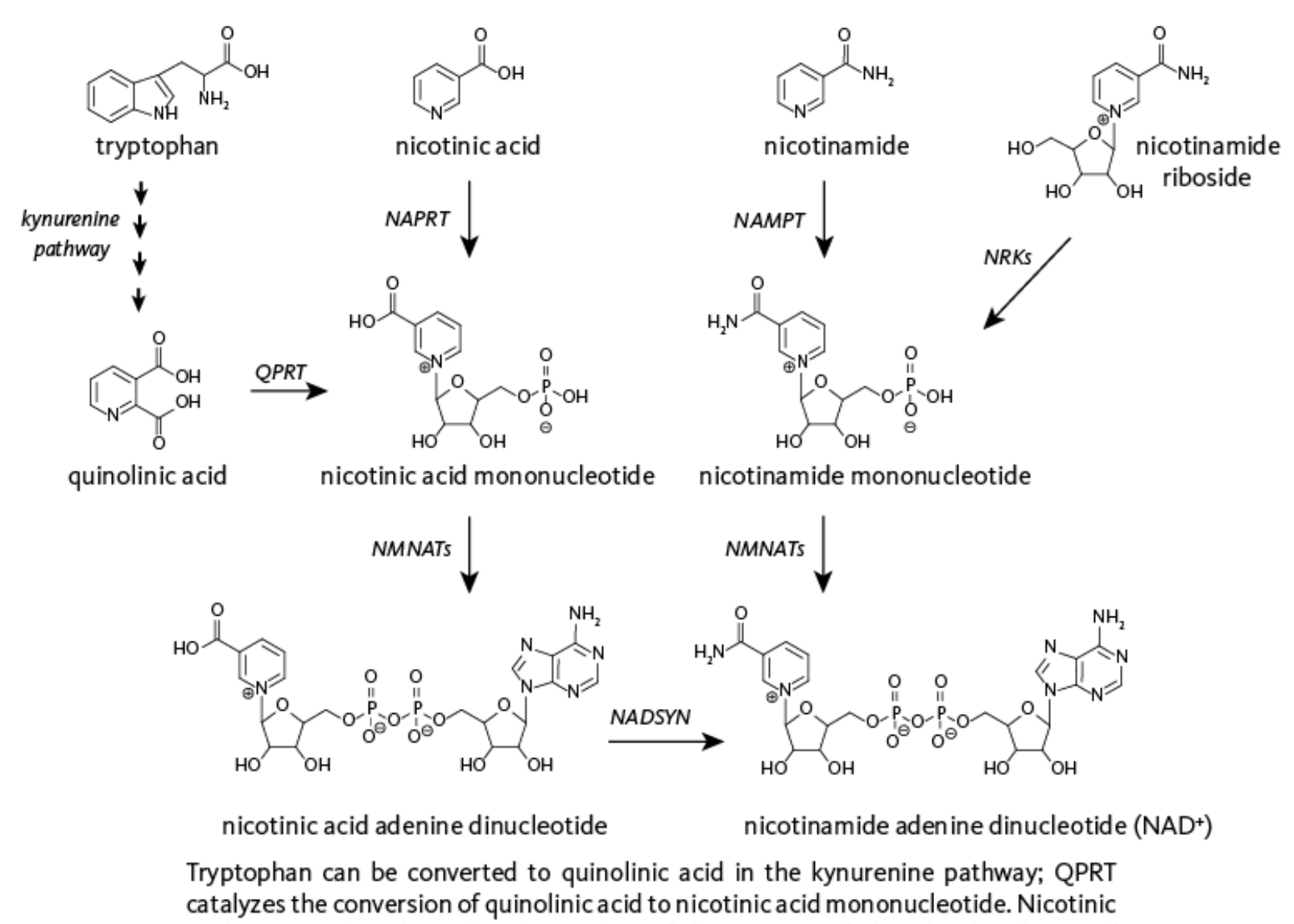

nicotinic acid
(pyridine-3-carboxylic acid;
often referred to as 'niacin')
nicotinamide
(pyridine-3-carboxamide, niacinamide)
tryptophan
nicotinamide
riboside

[Figure 1 - Click to Enlarge]

Figure 2 illustrates the separate biosynthetic pathways that lead to NAD$^+$ production from the various dietary precursors. NAD$^+$ is synthesized from nicotinamide and nicotinamide riboside via two enzymatic reactions, while the pathway that yields NAD$^+$ from nicotinic acid - known as the Preiss-Handler pathway — includes three steps. The kynurenine pathway is the longest NAD$^+$ biosynthetic pathway: the catabolism of tryptophan through kynurenine produces quinolinic acid, which is then converted to nicotinic acid mononucleotide, an intermediate in NAD$^+$ metabolism. NAD$^+$ is then synthesized from nicotinic acid mononucleotide in the Preiss-Handler pathway (2).

All pathways generate intermediary mononucleotides — either nicotinic acid mononucleotide or nicotinamide mononucleotide. Specific enzymes, known as phosphoribosyltransferases, catalyze the addition of a phosphoribose moiety onto nicotinic acid or quinolinic acid to produce nicotinic acid mononucleotide or onto nicotinamide to generate nicotinamide mononucleotide. Nicotinamide mononucleotide is also generated by the phosphorylation of nicotinamide riboside, catalyzed by nicotinamide riboside kinases (NRKs). Further, adenylyltransferases catalyze the adenylation of these mononucleotides to form either nicotinic acid adenine dinucleotide or NAD$^+$. Nicotinic acid adenine dinucleotide is then converted to NAD$^+$ by glutamine-dependent NAD$^+$ synthetase (NADSYN), which uses glutamine as an amide group donor (**Figure 2**) (2). Of note, nicotinic acid adenine dinucleotide has been reported to form following the administration of high-dose nicotinamide riboside, suggesting that a potential deamidation could occur to convert NAD$^+$ to nicotinic acid adenine dinucleotide when the pool of NAD$^+$ is high (1).

Figure 2. Synthesis of Nicotinamide Adenine Dinucleotide (NAD$^+$)

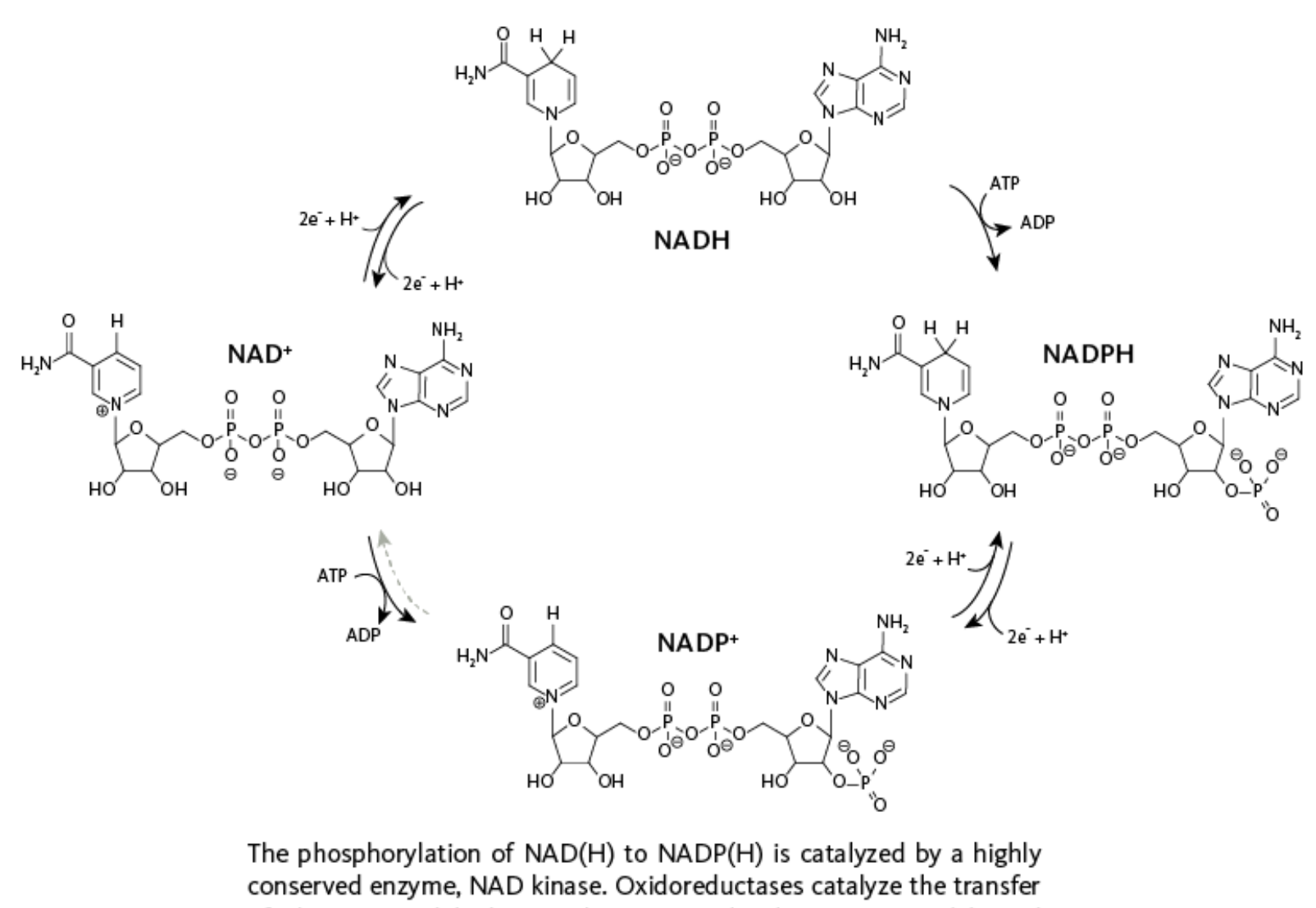

tryptophan
nicotinic acid
nicotinamide
nicotinamide riboside
kynurenine pathway
NAPRT
NAMPT
NRKs
QPRT
quinolinic acid
nicotinic acid mononucleotide
nicotinamide mononucleotide
NMNATs
NMNATs
NADSYN
nicotinic acid adenine dinucleotide
nicotinamide adenine dinucleotide (NAD+)

Tryptophan can be converted to quinolinic acid in the kynurenine pathway; QPRT catalyzes the conversion of quinolinic acid to nicotinic acid mononucleotide. Nicotinic acid mononucleotide is also the product of the reaction of phosphoribosylation of nicotinic acid catalyzed by NAPRT. Nicotinic acid mononucleotide is then converted to nicotinic acid adenine dinucleotide in a reaction catalyzed by NMNATs; NADSYN catalyzes the amidation of nicotinic acid adenine dinucleotide into NAD$^+$. Both nicotinamide and nicotinamide riboside are precursors of nicotinamide mononucleotide. The adenylation of nicotinamide mononucleotide catalyzed by NMNATs produces NAD$^+$. *NADSYN, Nicotinamide adenine dinucleotide synthase; NAMPT, Nicotinamide phosphoribosyltransferase; NAPRT, Nicotinic acid phosphoribosyltransferase; NMNATs, Nicotinamide mononucleotide adenylyltransferase; NRKs, Nicotinamide riboside kinases; QPRT, Quinolinate phosphoribosyltransferase.*

[Figure 2 - Click to Enlarge]

NAD kinase catalyzes the phosphorylation of NAD into NADP using adenosyl triphosphate (ATP) as the phosphoryl donor (3). The oxidation-reduction (redox) properties of the dinucleotide are not affected by the phosphorylation such that the redox pairs NAD$^+$/NADH and NADP$^+$/NADPH show similar redox potentials (4). Oxidation and reduction of the C-4 position of the nicotinamide moiety of NADand its phosphorylated form are essential for electron-transfer reactions supporting vital metabolic and bioenergetic functions in all cells (see Function). Thus, NAD and NADP are recycled back and forth between oxidized (NAD$^+$ and NADP$^+$) and reduced forms (NADH and NADPH), as shown in **Figure 3**.

Figure 3. NAD(P) Oxido-reduction Balance



The phosphorylation of NAD(H) to NADP(H) is catalyzed by a highly conserved enzyme, NAD kinase. Oxidoreductases catalyze the transfer of electrons and hydrogens between molecules using NAD(P)$^+$ and NAD(P)H as electron acceptors and donors, respectively. Thus, in electron-transfer reactions, dinucleotides are recycled back and forth between their oxidized (NAD$^+$ and NADP$^+$) and reduced (NADH and NADPH) forms.

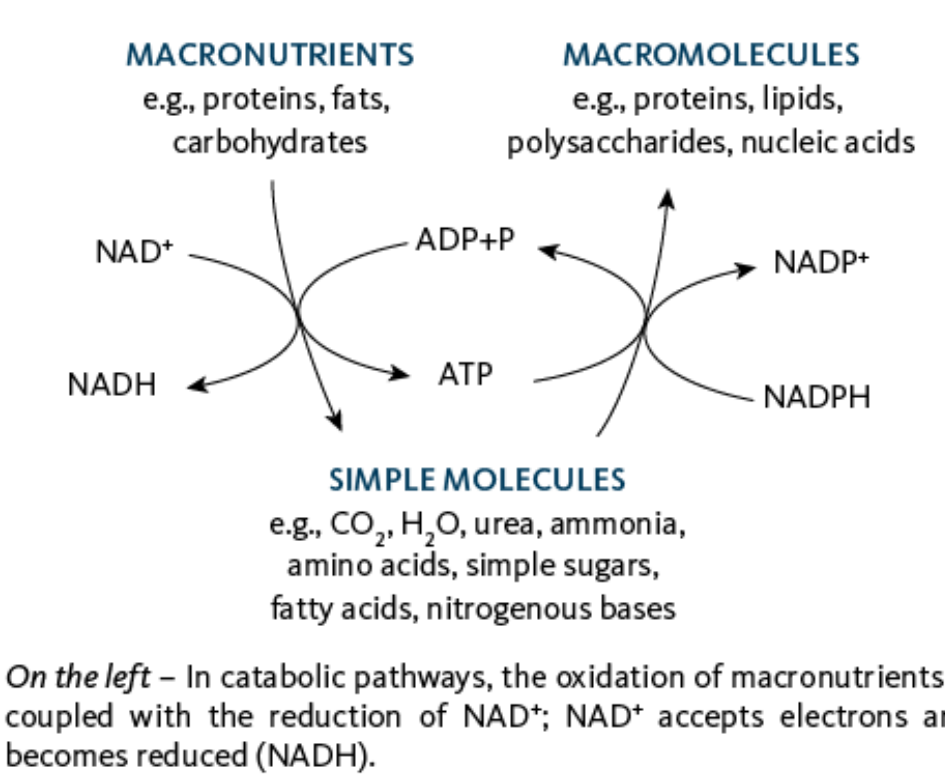
[Figure 3 - Click to Enlarge]

Function

NAD as a coenzyme in electron-transfer reactions

Living organisms derive most of their energy from redox reactions, which are processes involving the transfer of electrons. Over 400 enzymes require the niacin coenzymes, NAD and NADP, mainly to accept or donate electrons for redox reactions (5). NAD and NADP appear to support distinct functions (**Figure 4**). NAD functions most often in energy-producing reactions involving the degradation (catabolism) of carbohydrates, fats, proteins, and alcohol. NADP generally serves in biosynthetic (anabolic) reactions, such as in the synthesis of fatty acids, steroids (e.g., cholesterol, bile acids, and steroid hormones), and building blocks of other macromolecules (4). NADP is also essential for the regeneration of components of detoxification and antioxidant systems (4). To support these functions, the cell maintains NAD in a largely oxidized state (NAD$^+$) to serve as oxidizing agent for catabolic reactions, while NADP is kept largely in a reduced state (NADPH) to readily donate electrons for reductive cellular processes (4, 6).

Figure 4. Simplified Overview of NAD/NADP Function in Catabolic and Anabolic Pathways


MACRONUTRIENTS
e.g., proteins, fats, carbohydrates
MACROMOLECULES
e.g., proteins, lipids, polysaccharides, nucleic acids
NAD+
NADH
ADP+P
ATP
NADP+
NADPH
SIMPLE MOLECULES
e.g., CO2, H2O, urea, ammonia, amino acids, simple sugars, fatty acids, nitrogenous bases

On the left – In catabolic pathways, the oxidation of macronutrients is coupled with the reduction of NAD$^+$; NAD$^+$ accepts electrons and becomes reduced (NADH).
On the right – In anabolic pathways, the oxidation of NADPH provides electrons needed for the biosynthesis of macromolecules; NADPH donates electrons and becomes oxidized (NADP$^+$).

[Figure 4 - Click to Enlarge]

NAD as a substrate for NAD-consuming enzymes

The niacin coenzyme, NAD, is the substrate (reactant) for at least four classes of enzymes. Two classes of enzymes with mono adenosine diphosphate (ADP)-ribosyltransferase and/or poly (ADP-ribose) polymerase activities catalyze ADP-ribosyl transfer reactions. Silent information regulator-2 (Sir2)-like proteins (sirtuins) catalyze the removal of acetyl groups from acetylated proteins, utilizing ADP-ribose from NAD as an acceptor for acetyl groups. Finally, ADP-ribosylcyclases are involved in the regulation of intracellular calcium signaling.

ADP-ribosylation

Enzymes with ADP-ribosyltransferase activities were formerly divided between mono ADP-ribosyltransferases (ARTs) and poly (ADP-ribose) polymerases (PARPs). ARTs were first discovered in certain pathogenic bacteria — like those causing cholera or diphtheria — where they mediate the actions of toxins. These enzymes transfer an ADP-ribose residue moiety from NAD to a specific amino acid of a target protein, with the creation of an ADP-ribosylated protein and the release of nicotinamide.

Because most PARPs have been found to exhibit only mono ADP-ribosyltransferase activities, a new nomenclature was proposed for enzymes catalyzing ADP-ribosylation: A family of mono ADP-ribosyltransferases with homology to bacterial diphteria toxins was named ARTD, while enzymes with either mono or poly ADP-ribosyltransferase activities and related to C2 and C3 clostridial toxins were included in the ARTC family (7, 8).

- **ARTCs** are extracellular enzymes that catalyze the mono ADP-ribosylation of membrane or secreted proteins involved in innate immunity and cell communication (2).
- **ARTDs** are intracellular enzymes with either mono or poly ADP-ribosyltransferase activities. At least 18 ARTDs have been identified. All ARTDs possess a diphtheria toxin-like catalytic domain that binds NAD$^+$. Only ARTDs 1, 2, 5, and 6 catalyze poly (ADP-ribose) transfers; the others have mono ADP-ribosyltransferase activities. ARTDs were shown to be involved in DNA repair and stress responses, cell signaling, transcription regulation, apoptosis, cell differentiation, maintenance of genomic integrity, and antiviral defense (reviewed in 8).

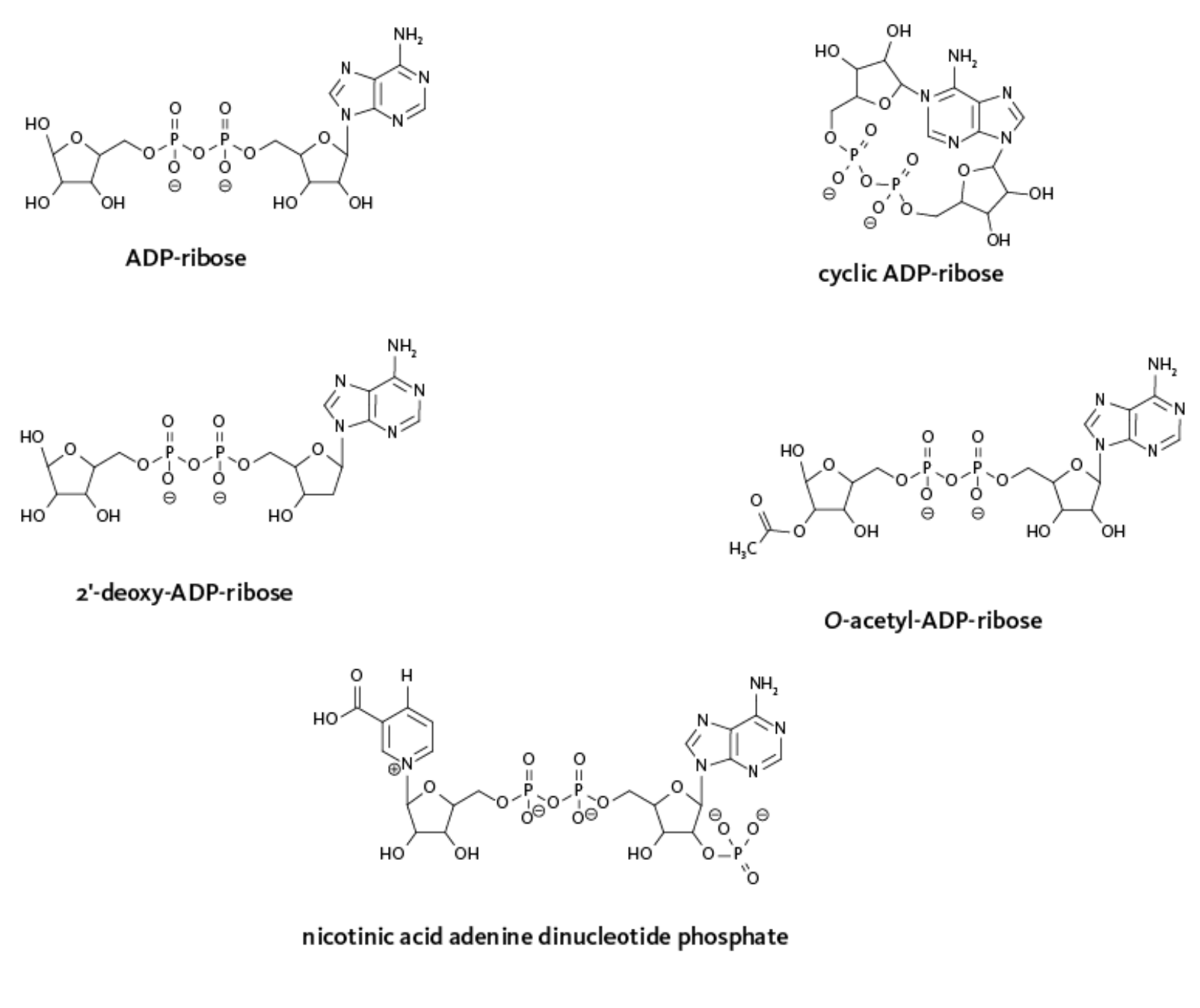
NAD-dependent deacetylation

Seven **sirtuins** (SIRT 1-7) have been identified in humans. Sirtuins are a class of NAD-dependent deacetylase enzymes that remove acetyl groups from the acetylated lysine residues of target proteins. During the deacetylation process, the acetyl group is transferred onto the ADP-ribose moiety cleaved off NAD, producing O-acetyl-ADP-ribose. Nicotinamide can exert feedback inhibition to the deacetylation reaction (9). Like ADP-ribosylation, acetylation is a post-translational modification that affects the function of target proteins. The initial interest in sirtuins followed the discovery that their activation could mimic caloric restriction, which has been shown to increase lifespan in lower organisms. Such a role in mammals is controversial, although sirtuins are energy-sensing regulators involved in signaling pathways that could play important roles in delaying the onset of age-related diseases (e.g., cardiovascular disease, cancer, dementia, arthritis). To date, the spectrum of their biological functions includes gene silencing, DNA damage repair, cell cycle regulation, and cell differentiation (10).

Calcium mobilization

In humans, CD38 and CD157 belong to a family of **NAD$^+$ glycohydrolases/ADP-ribosylcyclases**. These enzymes catalyze the formation of key regulators of calcium signaling, namely (linear) ADP-ribose, cyclic ADP-ribose, and nicotinic acid adenine dinucleotide phosphate (**Figure 5**). Cyclic ADP-ribose and nicotinic acid adenine dinucleotide phosphate works within cells to provoke the release of calcium ions from internal storage sites (i.e., endoplasmic reticulum, lysosomes, mitochondria), whereas ADP-ribose stimulates extracellular calcium entry through cell membrane TRPM2 cation channels (2). Another TRPM2 agonist, 2'-deoxy-ADP-ribose, was recently identified *in vitro*. CD38 was found to catalyze the synthesis of 2'-deoxy-ADP-ribose from nicotinamide mononucleotide and 2'-deoxy-ATP (11). *O*-acetyl-ADP-ribose generated by the activity of sirtuins also controls calcium entry through TRPM2 channels (6). Intracellular calcium-mediated signal transduction is regulated by transient calcium entry into the cell or release of calcium from intracellular stores. Calcium signaling is critically involved in processes like neurotransmission, insulin release from pancreatic β-cells, muscle cell contraction, and T-lymphocyte activation (6).

Figure 5. Calcium-mobilizing Derivatives of Niacin



[Figure 5 - Click to Enlarge]

NAD as a ligand

NAD$^+$ has been identified as an endogenous agonist of purinergic membrane receptors of the P2Y subclass. In particular, NAD was found to bind to P2Y1 receptor and act as an inhibitory neurotransmitter at neuromuscular junctions in visceral smooth muscles (12). Extracellular NAD$^+$ was also found to behave like a proinflammatory cytokine, triggering the activation of isolated granulocytes. NAD$^+$ binding to the P2Y11 receptor at the granulocyte surface activated a signaling cascade involving cyclic ADP-ribose and the rise of intracellular calcium, eventually stimulating superoxide generation and chemotaxis (13). Similar observations were made with lipopolysaccharide-activated monocytes (14). Extracellular NAADP$^+$ and ADP-ribose might also bind to P2Y receptors and trigger intracellular NAADP$^+$- and ADP-ribose-dependent calcium mobilization (see Calcium mobilization) (15, 16).

Lipid-lowering effects with pharmacologic doses of nicotinic acid

For over half a century, pharmacologic doses of nicotinic acid, but not nicotinamide, have been known to reduce serum cholesterol (see Disease Treatment) (17). However, the exact mechanisms underlying the lipid-lowering effect of nicotinic acid remain speculative. Two G-protein-coupled membrane receptors, GPR109A and GPR109B, bind nicotinic acid with high and low affinity, respectively. These nicotinic acid receptors are primarily expressed in adipose tissue and immune cells (but not lymphocytes). They are also found in retinal pigmented and colonic epithelial cells, keratinocytes, breast cells, microglia, and possibly at low levels in the liver (18). Thus, lipid-modifying effects of nicotinic acid are likely to be mediated by receptor-independent mechanisms in major tissues of lipid metabolism like liver and skeletal muscle. Early *in vitro* data suggested that nicotinic acid could impair very-low-density lipoprotein (VLDL) secretion by inhibiting triglyceride synthesis and triggering ApoB lipoprotein degradation in hepatocytes (19). In another study, nicotinic acid affected the hepatic uptake of ApoAI lipoprotein, thereby reducing high-density lipoprotein (HDL) removal from the circulation (reviewed in 20). In adipocytes, the binding of nicotinic acid to GPR109A was found to initiate a signal transduction cascade resulting in reductions in free fatty acid production via the inhibition of hormone-sensitive lipase involved in triglyceride lipolysis (21). Nonetheless, recent observations have suggested that the lipid-lowering effect of nicotinic acid was not due to its anti-lipolytic activity (22). Trials showed that synthetic agonists of GPR109A acutely lowered free fatty acids yet failed to affect serum lipids (22). Aside from its impact on HDL and other plasma lipids, nicotinic acid has exhibited anti-atherosclerotic activities in cultured monocytes, macrophages, or vascular endothelial cells, by modulating inflammation and oxidative stress and regulating cell adhesion, migration, and differentiation (reviewed in 18).

Deficiency

Pellagra

Causes

The late stage of severe niacin deficiency is known as pellagra. Early records of pellagra followed the widespread cultivation of corn in Europe in the 1700s (23). The disease is generally associated with poorer social classes whose chief dietary staple consisted of cereal like corn or sorghum. Pellagra was also common in the southern United States during the early 1900s where income was low and corn products were a major dietary staple (24). Interestingly, pellagra was not known in Mexico, where corn was also an important dietary staple and much of the population was also poor. In fact, if corn contains appreciable amounts of niacin, it is present in a bound form that is not nutritionally available to humans. The traditional preparation of corn tortillas in Mexico involves soaking the corn in a lime (calcium oxide) solution, prior to cooking. Heating the corn in an alkaline solution results in the release of bound niacin, increasing its bioavailability (25). Pellagra epidemics were also unknown to Native Americans who consumed immature corn that contains predominantly unbound (bioavailable) niacin (24).

Niacin deficiency or pellagra may result from inadequate dietary intake of NAD precursors, including tryptophan. Niacin deficiency — often associated with malnutrition — is observed in the homeless population, in individuals suffering from anorexia nervosa or obesity, and in consumers of diets high in maize and poor in animal protein (26-29). Deficiencies of other B vitamins and some trace minerals may aggravate niacin deficiency (30, 31). Malabsorptive disorders that can lead to pellagra include Crohn's disease and megaduodenum (32, 33). Patients with Hartnup's disease, a hereditary disorder resulting in defective tryptophan absorption, have developed pellagra (see Niacin-responsive genetic disorders). Carcinoid syndrome, a condition of increased secretion of serotonin and other catecholamines by carcinoid tumors, may also result in pellagra due to increased utilization of dietary tryptophan for serotonin rather than niacin synthesis. Further, prolonged treatment with the anti-tuberculosis drug isoniazid has resulted in niacin deficiency (34). Other pharmaceutical agents, including the immunosuppressive drugs azathioprine (Imuran) and 6-mercaptopurine, the anti-cancer drug 5-fluorouracil (5-FU, Adrucil), and levodopa/carbidopa (Sinemet; two drugs given to people with Parkinson's disease), are known to increase the reliance on dietary niacin by interfering with the tryptophan-kynurenine-niacin pathway (35). Finally, other populations at risk for niacin deficiency include dialysis patients, cancer patients (36, 37), individuals suffering from chronic alcoholism (38), and people with HIV (see HIV/AIDS below). Further, chronic alcohol intake can lead to severe niacin deficiency through reducing dietary niacin intake and interfering with the tryptophan-to-NAD conversion (30).

Symptoms of deficiency

The most common symptoms of niacin deficiency involve the skin, the digestive system, and the nervous system. The symptoms of pellagra are commonly referred to as the three "Ds": sun-sensitive dermatitis, diarrhea, and dementia. A fourth "D," death, occurs if pellagra is left untreated (5). In the skin, a thick, scaly, darkly pigmented rash develops symmetrically in areas exposed to sunlight. In fact, the word "pellagra" comes from "*pelle agra*," the Italian phrase for rough skin. Symptoms related to the digestive system include inflammation of the mouth and tongue ("bright red tongue"), vomiting, constipation, abdominal pain, and ultimately, diarrhea. Gastrointestinal disorders and diarrhea contribute to the ongoing malnourishment of the patients. Neurologic symptoms include headache, apathy, fatigue, depression, disorientation, and memory loss and are more consistent with delirium than with the historically described dementia (38). Disease presentations vary in appearance since the classic triad rarely presents in its entirety. The absence of dermatitis, for example, is known as pellagra *sine* pellagra.

Treatment

To treat pellagra, the World Health Organization (WHO) recommends administering nicotinamide to avoid the flushing commonly caused by nicotinic acid (see Safety). Treatment guidelines suggest using 300 mg/day of oral nicotinamide in divided doses, or 100 mg/day administered parenterally in divided doses, for three to four weeks (37, 39). Because patients with pellagra often display additional vitamin deficiencies, administration of a vitamin B-complex preparation is advised (39).

The Recommended Dietary Allowance (RDA)

Niacin equivalent (NE)

The term "niacin equivalent" (NE) is used to describe the contribution to dietary intake of all the forms of niacin that are available to the body. In healthy individuals, less than 2% of dietary tryptophan is converted to NAD in the kynurenine pathway (40). The synthesis of NAD from tryptophan is fairly inefficient and depends on enzymes requiring vitamin B$_6$ and riboflavin, as well as a heme (iron)-containing enzyme. Nonetheless, tryptophan is essential as a precursor for NAD$^+$. Inherited defects in tryptophan transport and metabolism result in severe clinical disorders attributed to NAD$^+$ depletion (see Niacin-responsive genetic disorders). On average, 60 milligrams (mg) of tryptophan are considered to correspond to 1 mg of niacin or 1 mg of NE.

Daily recommended intakes

The recommended dietary allowance (RDA) for niacin is based on the prevention of deficiency. Pellagra can be prevented by about 11 mg NE/day, but 12 mg to 16 mg NE/day has been found to normalize the urinary excretion of niacin metabolites (breakdown products) in healthy young adults. Because pellagra represents severe deficiency, the Food and Nutrition Board (FNB) of the US Institute of Medicine chose to use the excretion of niacin metabolites as an indicator of niacin nutritional status rather than symptoms of pellagra (41). However, it has been argued that cellular NAD and NADP content may be more relevant indicators of niacin nutritional status (24).

Table 1. Recommended Dietary Allowance (RDA) for Niacin

Life Stage	Age	Males (mg NE*/day)	Females (mg NE/day)
Infants	0-6 months	2 (AI)	2 (AI)
Infants	7-12 months	4 (AI)	4 (AI)
Children	1-3 years	6	6
Children	4-8 years	8	8
Children	9-13 years	12	12
Adolescents	14-18 years	16	14
Adults	19 years and older	16	14
Pregnancy	all ages	-	18
Breast-feeding	all ages	-	17
*NE, niacin equivalent: 1 mg NE = 60 mg of tryptophan = 1 mg niacin			

Disease Prevention

Cancer

Studies of cultured cells (*in vitro*) provide evidence that NAD content influences mechanisms that maintain genomic stability. Loss of genomic stability, characterized by a high rate of damage to DNA and chromosomes, is a hallmark of cancer (42). The current understanding is that the pool of NAD is decreased during niacin deficiency and that it affects the activity of NAD-consuming enzymes rather than redox and metabolic functions (43). Among NAD-dependent reactions, poly ADP-ribosylations catalyzed by PARP enzymes (ARTDs) are critical for the cellular response to DNA injury. After DNA damage, PARPs are activated; the subsequent poly ADP-ribosylations of a number of signaling and structural molecules by PARPs were shown to facilitate DNA repair at DNA strand breaks (44). Cellular depletion of NAD has been found to decrease levels of the tumor suppressor protein p53, a target for poly ADP-ribosylation, in human breast, skin, and lung cells (45). The expression of p53 was also altered by niacin deficiency in rat bone marrow cells (46). Impairment of DNA repair caused by niacin deficiency could lead to genomic instability and drive tumor development in rat models (47, 48). Both PARPs and sirtuins have been recently involved in the maintenance of heterochromatin, a chromosomal domain associated with genome stability, as well as in transcriptional gene silencing, telomere integrity, and chromosome segregation during cell division (49, 50). Neither the cellular NAD content nor the dietary intake of NAD precursors necessary for optimizing protective responses following DNA damage has been determined, but both are likely to be higher than that required for the prevention of pellagra.

Bone marrow

Cancer patients often suffer from bone marrow suppression following chemotherapy, given that bone marrow is one of the most proliferative tissues in the body and thus a primary target for chemotherapeutic agents. Niacin deficiency was found to decrease bone marrow NAD and poly-ADP-ribose levels and increase the risk of chemically induced leukemia in rats (51). Conversely, a pharmacologic dose of either nicotinic acid or nicotinamide was able to increase NAD and poly ADP-ribose in bone marrow and decrease the development of leukemia in rats (52). It has been suggested that niacin deficiency often observed in cancer patients could sensitize bone marrow tissue to the suppressive effect of chemotherapy. However, little is known regarding cellular NAD levels and the prevention of DNA damage or cancer in humans. One study in two healthy individuals involved elevating NAD levels in blood lymphocytes by supplementation with 100 mg/day of nicotinic acid for eight weeks. Compared to non-supplemented individuals, the supplemented individuals had reduced DNA strand breaks in lymphocytes exposed to free radicals in a test tube assay (53). However, nicotinic acid supplementation of up to 100 mg/day for 14 weeks in 21 healthy smokers failed to provide any evidence of a decrease in cigarette smoke-induced genetic damage in blood lymphocytes compared to placebo (54). More recently, the frequency of chromosome translocation was used to evaluate DNA damage in peripheral blood lymphocytes of 82 pilots chronically exposed to ionizing radiation, a known human carcinogen. In this observational study, the rate of chromosome aberrations was significantly lower in subjects with higher (28.4 mg/day) compared to lower (20.5 mg/day) dietary niacin intake (55). Higher availability of NAD$^+$ in X-irradiated peripheral blood lymphocytes was found to favor DNA repair by enhancing survival, particularly through SIRT-mediated p53 deacetylation (56).

Upper digestive tract

Generally, relationships between dietary factors and cancer are established first in epidemiological studies and followed up by basic cancer research at the cellular level. In the case of niacin, research on biochemical and cellular aspects of DNA repair has stimulated an interest in the relationship between niacin intake and cancer risk in human populations (57). A large case-control study found increased consumption of niacin, along with antioxidant nutrients, to be associated with decreased incidence of oral (mouth), pharyngeal (throat), and esophageal cancers in northern Italy and Switzerland. An increase in daily niacin intake of 6.2 mg was associated with about a 40% decrease in cases of cancers of the mouth and throat, while a 5.2 mg increase in daily niacin intake was associated with a similar decrease in cases of esophageal cancer (58, 59).

Skin

Niacin deficiency can lead to severe sunlight sensitivity in exposed skin. Given the implication of NAD-dependent enzymes in DNA repair, there has been some interest in the effect of niacin on skin health. *In vitro* and animal experiments have helped gather information, but human data on niacin/NAD status and skin cancer are very limited. One study reported that niacin supplementation decreased the risk of ultraviolet light (UV)-induced skin cancers in mice, despite the fact that mice convert tryptophan to NAD more efficiently than rats and humans and thus do not get severely deficient (60). Hyper-proliferation and impaired differentiation of skin cells can alter the integrity of the skin barrier and increase the occurrence of pre-malignant and malignant skin conditions. A protective effect of niacin was suggested by topical application of myristyl nicotinate, a niacin derivative, which successfully increased the expression of epidermal differentiation markers in subjects with photodamaged skin (61). The activation of the nicotinic acid receptors, GPR109A and GPR109B, by pharmacologic doses of niacin could be involved in improving skin barrier function. Conversely, differentiation defects in skin cancer cells were linked to the abnormal cellular localization of defective nicotinic acid receptors (62). Nicotinamide restriction with subsequent depletion of cellular NAD was shown to increase oxidative stress-induced DNA damage in a precancerous skin cell model, implying a protective role of NAD-dependent pathways in cancer (63). Altered NAD availability also affects sirtuin expression and activity in UV-exposed human skin cells. Along with PARPs, NAD-consuming sirtuins could play an important role in the cellular response to photodamage and skin homeostasis (64).

A pooled analysis of two large US prospective cohort studies that followed 41,808 men and 72,308 women for up to 26 years suggested that higher versus lower intake of niacin (from diet and supplements) might be protective against squamous-cell carcinoma but not against basal-cell carcinoma and melanoma (65). A phase III, randomized, double-blind, placebo-controlled trial in 386 subjects with a history of nonmelanoma skin cancer recently examined the effect of daily nicotinamide supplementation (1 g) for 12 months on skin cancer recurrence at three-month intervals over an 18-month period (66). Nicotinamide effectively reduced the rate of premalignant actinic keratose (-11%), squamous-cell carcinoma (-30%), and basal-cell carcinoma (-20%) compared to placebo after 12 months, yet this protection was not sustained during the six-month post-supplementation period (66). Larger trials are needed to assess whether nicotinamide could reduce the risk of melanomas, which are not as common as other skin cancer but are more deadly (67).

Type 1 diabetes mellitus

Type 1 diabetes mellitus in children is caused by the autoimmune destruction of insulin-secreting β-cells in the pancreas. Prior to the onset of symptomatic diabetes, specific antibodies, including islet cell autoantibodies (ICA), can be detected in the blood of high-risk individuals (68). In an experimental animal model of diabetes, high levels of nicotinamide are administered to protect β-cells from damage caused by streptozotocin (69).

Yet, pharmacologic doses of nicotinamide (up to 3 g/day) have not been found to be effective in delaying or preventing the onset of type 1 diabetes in at-risk subjects. An analysis of 10 trials, of which five were placebo-controlled, found evidence of improved β-cell function after one year of treatment with nicotinamide, but the analysis failed to find any clinical evidence of improved glycemic control (70). A large, multicenter randomized controlled trial of nicotinamide in ICA-positive siblings (ages, 3-12 years) of type 1 diabetic patients also failed to find a difference in the incidence of type 1 diabetes after three years (70). A randomized, double-blind, placebo-controlled multicenter trial of nicotinamide (maximum of 3 g/day) was conducted in 552 ICA-positive relatives of patients with type 1 diabetes. The proportion of relatives who developed type 1 diabetes within five years was comparable whether they were treated with nicotinamide or placebo (71). Nicotinamide could reduce inflammation-related parameters in these high-risk subjects yet was ineffective to prevent disease onset (72). More recently, case reports of the combined use of nicotinamide (25 mg/kg/day) and acetyl-L-carnitine (50 mg/kg/day) in children at risk for type 1 diabetes showed promising results, warranting further investigation (73).

Disease Treatment

Niacin supplements at pharmacologic doses (i.e., doses much larger than those needed to prevent deficiency) have been used in an attempt to treat a range of conditions, some of which are discussed below.

Niacin-responsive genetic disorders

Congenital NAD deficiency-related disorders can result from mutations in genes involved in the uptake and transport of the various dietary NAD$^+$ precursors or in the distinct metabolic pathways leading to NAD$^+$ production (see Metabolism). Some of these disorders might respond to niacin supplementation. For example, defective transport of tryptophan into cells results in Hartnup disease, which features signs of severe niacin deficiency (74). Hartnup disease is due to mutations in the *SLCA19* gene, which codes for a sodium-dependent neutral amino acid transporter expressed primarily in the kidneys and intestine. Disease management involves supplementation with nicotinic acid or nicotinamide (75). Recessive mutations in genes coding for enzymes of the kynurenine pathway — namely kynureninase and 3-hydroxyanthranilic-acid 3,4-dioxygenase — lead to combined vertebral, anal, cardiac, tracheo-esophageal, renal, and limb (VACTERL) congenital malformations (76). Depletion of NAD$^+$, rather than accumulation of intermediate metabolites in the kynurenine pathway, was found to be responsible for these malformations. Niacin supplementation throughout pregnancy ensured adequate levels of NAD$^+$ and prevented congenital anomalies in mice with kynurenine pathway mutations (76). In humans, the dose of NAD$^+$ precursors necessary to avert NAD deficiency-induced congenital VACTERL malformations has yet to be defined (77).

Nicotinamide may also rescue NAD$^+$ depletion secondary to an ultra-rare inborn error of glutamine metabolism (78). Glutamine is required for the conversion of nicotinic acid adenine dinucleotide to NAD$^+$ catalyzed by NAD$^+$ synthetase (**Figure 2**). Thus, inherited glutamine synthetase deficiency specifically affects the synthesis of NAD$^+$ from the NAD$^+$ precursors, tryptophan and nicotinic acid. If the combined deficiencies of glutamine and NAD$^+$ are responsible for the severe clinical phenotype of subjects with inherited glutamine synthetase deficiency, it is likely that supplementation with both glutamine and nicotinamide would provide some relief (78).

Finally, many inborn errors of metabolism result from genetic mutations decreasing cofactor binding affinity and, subsequently, enzyme efficiency (79). In many cases, the administration of high doses of the vitamins serving as precursors of cofactors can restore enzymatic activity — at least partially — and lessen signs of the genetic diseases (79). Given the large number of enzymes requiring NAD, it is speculated that many of the conditions due to defective enzymes might be rescued by niacin supplementation (5).

Cardiovascular disease

Cardiovascular risk factors

Nicotinic acid is a well-known lipid-lowering agent: Nicotinic acid therapy markedly increases high-density lipoprotein (HDL) cholesterol concentrations, decreases serum lipoprotein(a) concentrations, and shifts small, dense low-density lipoprotein (LDL) particles to large, buoyant LDL particles. All of these changes in the blood lipid profile are considered cardioprotective. Low concentrations of HDL-cholesterol are one major risk factor for coronary heart disease (CHD), and an increase in HDL concentrations is associated with a reduction of that risk (80). Because of the adverse side effects associated with high doses of nicotinic acid (see Safety), nicotinic acid has most often been used in combination with other lipid-lowering medications at slightly lower doses (17). In particular, low-dose nicotinic acid is often co-administered with 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins), the cornerstone of treatment of hyperlipidemia, a major risk factor for CHD. A placebo-controlled study in 39 patients taking statins (cerivastatin, atorvastatin, or simvastatin) found that a very low dose of nicotinic acid (100 mg/day) increased HDL-cholesterol by only 2.1 mg/dL, and the combination had no effect on LDL-cholesterol, total cholesterol, or triglyceride concentrations (81).

The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2 study — a double-blind, placebo-controlled trial — investigated the incremental effect of adding nicotinic acid (1 g/day) to statin therapy in 167 patients with known CHD and low HDL concentrations on carotid intima-media thickness (CIMT) (82), a surrogate endpoint for the development of atherosclerosis. The addition of extended-release nicotinic acid to simvastatin prevented the increase in CIMT compared to simvastatin monotherapy. A post-hoc analysis of data from ARBITER2 showed that the blockade of atherosclerotic progression was related to the increase in HDL concentrations in patients with normal glycemic status. However, in the presence of additional risk factors, such as impaired fasting glucose or diabetes mellitus, the increase in HDL concentrations was not predictive of CIMT reduction and atherosclerotic retardation (83). A comparative efficacy trial (ARBITER6) also showed a significant reduction of baseline CIMT with extended-release nicotinic acid (2 g/day for 14 months), as opposed to ezetimibe (a cholesterol-lowering drug), in patients taking statins (84).

Additional studies have examined the impact of nicotinic acid on endothelium-dependent brachial flow-mediated dilation (FMD) in patients at risk of CHD or with established CHD. The measurement of FMD is often used as a surrogate marker of endothelial function; FMD values are inversely correlated with the risk of future cardiovascular events (85). A meta-analysis of seven randomized controlled trials, including 441 participants, showed a significant, 2% increase with nicotinic acid (1-2 g/day) administered for 12 weeks to one year (86).

Cardiovascular events

Several randomized, placebo-controlled, multicenter trials have investigated the efficacy and safety of nicotinic acid therapy, alone or in combination with other lipid-lowering agents, on outcomes of cardiovascular disease (CVD). Specifically, the Coronary Drug Project (CDP) followed over 8,000 men with a previous myocardial infarction for six years (87). Compared to the placebo group, patients who took 3 g of immediate-release nicotinic acid daily experienced an average 10% reduction in total blood cholesterol, a 26% decrease in triglycerides, a 27% reduction in recurrent nonfatal myocardial infarction, and a 26% reduction in cerebrovascular events (stroke and transient ischemic attacks). In addition, nine-year follow-up post-trial revealed a 10% reduction in total deaths with nicotinic acid treatment.

The HDL-Atherosclerosis Treatment Study (HATS), a three-year randomized controlled trial in 160 patients with documented CHD and low HDL concentrations, found that a combination of simvastatin and nicotinic acid (2-3 g/day) increased HDL concentrations, inhibited the progression of coronary artery stenosis (narrowing), and decreased the frequency of cardiovascular events, including myocardial infarction and stroke, compared to placebo (88). A subgroup analysis of the HATS patients with metabolic syndrome showed a reduction in rate of primary clinical events even though glucose and insulin metabolism were moderately impaired by nicotinic acid (89). Moreover, a review of nicotinic acid safety and tolerability among the HATS subjects showed glycemic control in diabetic patients returned to pretreatment values following eight months of disease management with medication and diet (90). Similarly, the cardiovascular benefit of long-term nicotinic acid therapy outweighed the modest increase in risk of newly onset type 2 diabetes in patients from the CDP study (91).

In contrast, the AIM-HIGH (Atherothrombosis intervention in metabolic syndrome with low HDL/high triglycerides: impact on global health outcomes) trial, which examined the incremental effect of extended-release nicotinic acid (1.5-2 g/day) on 3,414 patients who had established CVD and atherogenic dyslipidemia and were treated with simvastatin (+/- ezetimibe), provided disappointing results. Indeed, in these patients who had achieved target concentrations of LDL-cholesterol (<70 mg/dL) before randomization, the HDL-raising effect of nicotinic acid treatment failed to reduce the number of cardiovascular events after a mean follow-up of three years (92, 93). While some limitations, like a greater use of simvastatin and ezetimibe in the control group, may have confounded the results, it was also suggested that low HDL-cholesterol might be a marker of risk rather than a causal risk factor for predicting CVD (93). In addition, a post-hoc analysis of 505 participants with stage 3 chronic kidney disease found an increase in all-cause mortality in those randomized to nicotinic acid compared to those in the placebo group (94).

Although nicotinic acid failed to reduce the number of cardiovascular events in simvastatin-treated patients with low LDL-cholesterol, these results cannot be extrapolated to patients with higher LDL-cholesterol at baseline. A much larger multicenter, randomized, double-blind, placebo-controlled trial — the HPS2-THRIVE (Heart protection study 2: treatment of HDL to reduce the incidence of vascular events) trial — in 25,673 participants with vascular disease examined the incremental effect of extended-release nicotinic acid (2 g/day) and laropiprant (a prostaglandin D2 receptor-1 antagonist; 40 mg/day) on the incidence of vascular events. Compared to placebo, nicotinic acid/laropiprant reduced LDL-cholesterol by an average of 10 mg/dL, decreased triglycerides by 33 mg/dL, and increased HDL-cholesterol by 6 mg/dL after a median 3.9-year follow-up period. Nonetheless, nicotinic acid/laropiprant showed no effect on the incidence of major vascular events and death of any cause (95).

A recent meta-analysis of 23 randomized controlled trials — including the CDP, AIM-HIGH, and HPS2-THRIVE trials — in 39,195 subjects with a history of vascular disease compared the effect of nicotinic acid alone or as an add-on to other lipid-lowering agents. No cardiovascular benefits were associated with nicotinic acid therapy: the number of fatal and non-fatal myocardial infarctions and strokes was not decreased with nicotinic acid supplementation (median dose of 2 g/day for a median period of 11.5 months) (96).

Despite the lack of evidence for a role of nicotinic acid in CVD prevention (96, 97), the use of nicotinic acid therapy has rapidly increased over the years in the US (98).

Friedreich's ataxia

Friedreich's ataxia, a common form of inherited ataxia, is an early onset recessive disorder with clinical features that includes progressive ataxia, scoliosis, dysarthria, cardiomyopathy, and diabetes mellitus (99). Most affected subjects carry homozygous guanine-adenine-adenine (GAA) repeat expansions in the first intron of the gene *FXN* coding for the protein frataxin. These abnormal and unstable GAA repeats trigger gene silencing through heterochromatin formation, leading to significantly reduced frataxin expression (100). Frataxin is a mitochondrial protein needed for the making of iron-sulfur clusters (ISC). ISC-containing subunits are especially important for the mitochondrial respiratory chain and for the synthesis of heme-containing proteins (99).

Predominantly localized in the nucleus, SIRT1 is a NAD$^+$-dependent deacetylase that promotes gene silencing through heterochromatin formation. Nicotinamide has been shown to antagonize heterochromatization of the *FXN* locus and upregulate frataxin expression in lymphoblastoid cells derived from Friedreich's ataxia-affected patients, possibly through inhibiting SIRT1 activity (100). In an open-label, dose escalating pilot trial in 10 adult patients with Friedreich's ataxia, single and repeated doses of nicotinamide (2-8 g) for up to eight weeks were found to be well tolerated (101). Repeated daily doses of 3.5 to 6 g of nicotinamide led to significant increases in frataxin concentration in peripheral white blood cells (101). Yet, no neurological improvements were reported, suggesting that the duration of the treatment was too short and/or the nervous system of the participants was unresponsive to increases in frataxin (102). To our knowledge, there is currently no ongoing trial designed to further investigate the effect of nicotinamide in Friedreich's ataxia-affected patients.

HIV/AIDS

The first step in the kynurenine pathway is catalyzed by the extrahepatic enzyme, indoleamine 2,3-dioxygenase (IDO), which is responsible for the oxidative cleavage of tryptophan. The chronic stimulation of tryptophan oxidation, mediated by an increased activity of IDO and/or inadequate dietary niacin intakes, is observed with the infection of human immunodeficiency virus (HIV), the virus that causes acquired immunodeficiency syndrome (AIDS). Interferon-gamma (IFN-γ) is a cytokine produced by cells of the immune system in response to infection. Through stimulating the enzyme IDO, IFN-γ increases the breakdown of tryptophan, thus supporting the finding that the average tryptophan concentration in blood is significantly lower in HIV patients compared to uninfected subjects (40). An increased degradation of tryptophan via the kynurenine pathway appears to coexist with intracellular niacin/NAD deficiency in HIV infection (103). An explanatory model for these paradoxical observations incriminates the oxidative stress induced by multiple nutrient deficiencies in HIV patients (103). In particular, the activation of PARP enzymes (ARTDs) by oxidative damage to DNA could be responsible for inducing niacin/NAD depletion (see Function). The breakdown of tryptophan would then be a compensatory response to inadequate niacin/NAD levels.

However, metabolites derived from the oxidation of tryptophan in the kynurenine pathway regulate specific T-lymphocyte subgroups. As mentioned above, circulating IFN-γ, but also viral and bacterial products, can activate IDO during HIV infection. The overstimulation of the tryptophan pathway has been involved in the loss of normal T-lymphocyte function, which characterizes HIV infection (104, 105). The increased IDO activity has been linked to the altered immune response that contributes to the persistence of HIV (104). Antiretroviral therapy (ART) only partially restores normal IDO activity, without normalizing it, yet induces viral suppression and CD4 T-cell recovery (106). In a monkey model for HIV infection, a partial and transient blockade of IDO with IDO inhibitor 1-methyl tryptophan proved ineffective to reduce the viral load in plasma and intestinal tissues beyond the level achieved by ART (107). At present, a better understanding of the role of kynurenine pathway and other NAD biosynthetic pathways during HIV infection is needed before the relevance and clinical implications of niacin supplementation in HIV treatment could be considered.

Nonetheless, pharmacologic doses of nicotinic acid have been shown to be well tolerated in HIV patients with hyperlipidemia (108). Abnormal lipid profiles observed in patients have been attributed to the HIV infection and to the highly active antiretroviral treatment (HAART) (109). Moreover, insulin resistance has been detected together with dyslipidemia in ART-treated patients (110). Cardiovascular disease (CVD) is the second most frequent cause of deaths in the HIV population, and the rate of CVD is predicted to increase further as patients are living longer due to successful antiretroviral therapies. As for the general population, statin-based therapy appears to benefit HIV patients in terms of atherogenic protection and CVD risk reduction, although contraindications exist due to drug interactions with ART. Other first-line treatments include lipid-lowering fibrates, which are preferred to nicotinic acid due to the increased risk of glucose intolerance and insulin resistance (111). Nevertheless, an unblinded, controlled pilot study showed that extended-release nicotinic acid (0.5-1.5 g/day for 12 weeks) could effectively improve endothelial function of the brachial artery in ART-treated HIV subjects with low HDL-cholesterol and no history of CVD (112). In addition, a combined treatment of fibrates, extended-release nicotinic acid (0.5-2 g/day), and lifestyle changes (low-fat diet and exercise) for 24 weeks was effective in normalizing lipid parameters in a cohort of 191 ART-treated patients. Increased risk of liver dysfunction was detected in subjects receiving both fibrates and niacin, but insulin sensitivity was not affected by nicotinic acid treatment given alone or when combined with fibrates (113). Another 24-week, open-label, uncontrolled trial in 99 ART-treated patients found that randomization to extended-release nicotinic acid (0.5-2 g/day) or fenofibrates increased blood HDL-cholesterol but did not reduce inflammatory markers or improve endothelial function when compared to baseline (114).

Schizophrenia

Schizophrenia is a neurologic disorder with unclear etiology that is diagnosed purely from its clinical presentation. Because neurologic disorders associated with pellagra resemble acute schizophrenia, niacin-based therapy for the condition was investigated during the 1950s-70s (reviewed in 115). The adjunctive use of nutrients like niacin to correct deficiencies associated with neurologic symptoms is called orthomolecular psychiatry (116). Such an approach has not been included in psychiatric practice; practitioners have instead relied solely on antipsychotic drugs to eliminate the clinical symptoms of schizophrenia. Nevertheless, recent scientific advances and new hypotheses on the benefit of nutrient supplementation in the treatment of psychiatric disorders have suggested the re-assessment of orthomolecular medicine by the medical community (117, 118).

Skin flushing is one major side effect of the therapeutic use of nicotinic acid and the primary reason for non-adherence to treatment (see Toxicity). Flushing is caused by the activation of phospholipase A2, an enzyme that stimulates the production of a specific lipid from the prostanoid family called prostaglandin D2. Prostaglandin D2, synthesized by antigen-presenting cells of the skin and mucosa (i.e., the Langerhans cells), can induce the dilation of blood vessels and trigger a flushing response. Interestingly, patients with schizophrenia tend not to flush following treatment with nicotinic acid. This blunted skin flushing response suggests abnormal prostanoid signaling in schizophrenic patients (119, 120). An association has been found between the altered niacin sensitivity and greater functional impairment in schizophrenic subjects (121), which supports other findings suggesting that altered lipid metabolism could critically impair brain development and contribute to the disease (122). Interestingly, blunted skin flushing responses are more prevalent in first-degree relatives of people with schizophrenia than in the general population, suggesting that reduced niacin sensitivity is a heritable trait within affected families (123).

Sources

Food sources

Good sources of niacin include yeast, meat, poultry, red fish (e.g., tuna, salmon), cereal (especially fortified cereal), legumes, and seeds. Milk, green leafy vegetables, coffee, and tea also provide some niacin (124). In plants, especially mature cereal grains like corn and wheat, niacin may be bound to sugar molecules in the form of glycosides, which significantly decrease its bioavailability (25).

In the United States, the average dietary intake of niacin is about 30 mg/day for young adult men and 20 mg/day for young adult women. In a sample of adults over the age of 60, men and women were found to have an average dietary intake of 21 mg/day and 17 mg/day, respectively (41). Some foods with substantial amounts of niacin are listed in **Table 2**, along with their niacin content in milligrams (mg). Food composition tables generally list niacin content without including niacin equivalents (NE) from tryptophan or any adjustment for niacin bioavailability. For more information on the nutrient content of specific foods, search USDA's FoodData Central database; data included in **Table 2** are from this database (125).

Table 2. Some Food Sources of Niacin

Food	Serving	Niacin (mg)
Chicken (light meat, cooked without skin)	3 ounces*	8.9
Tuna (light, canned, packed in water)	3 ounces	8.6
Turkey (light meat, cooked without skin)	3 ounces	9.9
Salmon (chinook, cooked)	3 ounces	8.5
Beef (90% lean, cooked)	3 ounces	4.4
Cereal (unfortified)	1 cup	5-7
Cereal (fortified)	1 cup	20-27
Peanuts (dry-roasted)	1 ounce	4.1
Pasta (enriched, cooked)	1 cup	1.9-2.4
Lentils (cooked)	1 cup	2.1
Lima beans (cooked)	1 cup	0.8
Bread (whole-wheat)	1 slice	1.4
Coffee (brewed)	1 cup	2
*A three-ounce serving of meat is about the size of a deck of cards.		

Supplements

Niacin supplements are available as nicotinamide or nicotinic acid. Nicotinamide is the form of niacin typically used in nutritional supplements and in food fortification. Nicotinic acid is available over the counter and with a prescription as a cholesterol-lowering agent (126). Nicotinic acid for anti-hyperlipidemic use is available in three formulations: immediate-release (crystalline) nicotinic acid (absorption time, 1-2 hrs), extended-release nicotinic acid (absorption time, 8-12 hrs), and sustained-release nicotinic acid (absorption time, >12 hrs) (127). At the pharmacologic dose required for cholesterol-lowering effects, the use of nicotinic acid should be approached as if it were a drug (see Safety). Individuals should only undertake cholesterol-lowering therapy with nicotinic acid under the supervision of a qualified health care provider in order to minimize potentially adverse effects and maximize therapeutic benefits.

Safety

Toxicity

Nicotinic acid

Common side effects of nicotinic acid include flushing, pruritus (severe itching of the skin), skin rashes, and gastrointestinal disturbances, such as nausea and vomiting (97). Transient episodes of low blood pressure (hypotension) and headache have also been reported. Hepatotoxicity (liver cell damage), including elevated liver enzymes and jaundice, has been observed at intakes as low as 750 mg/day of nicotinic acid (128). Although hepatitis has been observed with extended-release nicotinic acid at dosages as little as 500 mg/day for two months, almost all reports of severe hepatitis have been associated with doses of 3 to 9 g/day used to treat high cholesterol for months or years (41). It is unclear whether immediate-release (crystalline) nicotinic acid is less toxic to the liver than extended-release forms (41). Yet, immediate-release nicotinic acid is often used at higher doses than extended-release forms, and severe liver toxicity has occurred in individuals who substituted extended-release nicotinic acid for immediate-release nicotinic acid at equivalent doses (126). Large doses of nicotinic acid have been observed to impair glucose tolerance, likely because of a decrease in insulin sensitivity. Impaired glucose tolerance in susceptible (pre-diabetic) individuals could result in elevated blood glucose concentrations and clinical type 2 diabetes mellitus. An analysis of the HPS2-THRIVE trial (see Cardiovascular disease), using data from 17,374 participants without type 2 diabetes at baseline, found a significantly higher proportion of newly diagnosed cases among those randomized to nicotinic acid/laropiprant than to placebo (5.7% versus 4.3%) over a 3.9 year-period (95). Likewise, randomization to nicotinic acid/laropiprant significantly increased the risk of serious disturbances in diabetes control (leading to hospitalization) compared to placebo among 8,299 participants with diabetes at baseline (95). Elevated blood concentrations of uric acid, occasionally resulting in attacks of gout in susceptible individuals, have also been observed with high-dose nicotinic acid therapy (126). Niacin at doses of 1.5 to 5 g/day has resulted in a few case reports of blurred vision and other eye problems, which have generally been reversible upon discontinuation (41). People with abnormal liver function or a history of liver disease, diabetes, active peptic ulcer disease, gout, cardiac arrhythmias, inflammatory bowel disease, migraine headaches, or alcoholism may be more susceptible to the adverse effects of excess niacin intake than the general population (41).

Nicotinamide

Nicotinamide is generally better tolerated than nicotinic acid; it does not generally cause flushing (126). However, nausea, vomiting, and signs of liver toxicity (elevated liver enzymes, jaundice) have been observed at very high doses (≥10 g/day) (126).

Nicotinamide riboside

A study in 12 healthy subjects found that nicotinamide riboside at three single doses (100 mg, 300 mg, and 1,000 mg) safely increased blood NAD$^+$. Two of the participants self-reported skin flushing after taking the 300-mg dose, and two others reported feeling hot following intake of 1,000 mg of nicotinamide riboside (1). In a recent randomized, placebo-controlled trial in 120 healthy adults (ages, 60-80 years), daily supplementation with nicotinamide riboside (250 mg or 500 mg) and pterostilbene (a SIRT activator; 50 mg or 100 mg) for eight weeks showed a favorable side effect profile, with no evidence of higher incidence of adverse effects compared to placebo (129). Most recently, a randomized, placebo-controlled trial in 40 obese men (ages, 40-70 years) found that daily supplementation with nicotinamide riboside (2,000 mg/day divided into two daily dosages) for 12 weeks was associated with reports of only minor side effects, including excessive sweating, pruritus, and mild gastrointestinal symptoms like bloating (139).

The tolerable upper intake level (UL)

Flushing of the skin primarily on the face, arms, and chest is a common side effect of nicotinic acid and may occur initially at doses as low as 30 mg/day. Although flushing from nicotinamide is rare, the Food and Nutrition Board set the tolerable upper intake level (UL) for niacin (nicotinic acid and nicotinamide) at 35 mg/day in adults to avoid the adverse effect of flushing (41). Analysis of data from the US National Health and Nutrition Examination Survey (NHANES) 2003-2006 found that 15.8% of children and adolescents (ages 2-18 years) and 8.5% of adults (≥19 years) had total usual niacin intakes exceeding the UL (130). The UL applies to the general population and is not meant to apply to individuals who are being treated with a nutrient under medical supervision (e.g., high-dose nicotinic acid for elevated blood cholesterol concentrations).

Table 3. Tolerable Upper Intake Level (UL) for Niacin

Age Group	UL (mg/day)
Infants 0-12 months	Not possible to establish*
Children 1-3 years	10
Children 4-8 years	15
Children 9-13 years	20
Adolescents 14-18 years	30
Adults 19 years and older	35
*Source of intake should be from food and formula only.	

Drug interactions

The occurrence of rhabdomyolysis is increased in patients treated with statins (HMG-CoA reductase inhibitors). Rhabdomyolysis is a relatively uncommon condition in which muscle cells are broken down, releasing enzymes and electrolytes into the blood, and sometimes resulting in kidney failure (131). Co-administration of nicotinic acid with a statin seems to enhance the risk of rhabdomyolosis (132). A new drug, laropiprant, blocks prostanoid receptors and reduces nicotinic acid-induced flushing (133). A randomized, placebo-controlled trial was designed to identify possible adverse effects of the niacin/laropiprant combination in over 25,000 simvastatin-treated subjects (134). When added to the statin therapy, niacin/laropiprant increased the risk of myopathy and rhabdomyolosis, particularly in Asian subjects. It is possible that the niacin/laropiprant combination further reduces the poor tolerability to statin treatment observed in certain populations (135).

In the three-year, randomized controlled HATS study, concurrent therapy with antioxidants (1,000 mg/day of vitamin C, 800 IU/day of *RRR*-α-tocopherol, 100 μg/day of selenium, and 25 mg/day of β-carotene) diminished the protective effects of the simvastatin-nicotinic acid combination (136). Although the mechanism for these effects is not known, the benefit of concurrent antioxidant therapy in patients on lipid-lowering agents has been questioned (137).

Adverse effects of large doses of nicotinic acid may be exacerbated by the concomitant use of certain medications. The risk of myopathy may be further increased in those taking nicotinic acid and bile acid sequestrants (e.g., cholestyramine, colestipol) or the anti-lipidemic drug, gemfibrozil (Lopid), and the risk of hepatotoxicity observed with nicotinic acid might be enhanced by drugs like paracetamol, amiodarone (Cordarone), or carbamazepine (Tegretol) (35). In addition, large doses of nicotinic acid may reduce uric acid excretion, thereby opposing the action of uricosuric agents like probenecid (Probalan) (35).

Several other medications may interact with niacin therapy or with absorption and metabolism of the vitamin (126). Estrogen and estrogen-containing oral contraceptives increase the efficiency of niacin synthesis from tryptophan, resulting in a decreased dietary requirement for niacin (138). Long-term administration of chemotherapy agents has been reported to cause symptoms of pellagra; therefore, niacin supplementation may be needed (see Pellagra causes).

Linus Pauling Institute Recommendation

The optimum intake of niacin for health promotion and chronic disease prevention is not yet known. The RDA (16 mg NE/day for men and 14 mg NE/day for women) is easily obtainable by consuming a varied diet and should prevent deficiency in most people. Following the Linus Pauling Institute recommendation to take a daily multivitamin/mineral supplement, containing 100% of the Daily Value (DV) for niacin, will provide at least 20 mg of niacin daily.

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Pantothenic Acid

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Summary

- Pantothenic acid — also known as vitamin B_5 — is a water-soluble vitamin that is a precursor in the synthesis of coenzyme A. Coenzyme A is essential to many biochemical reactions that sustain life. Also, the phosphopantetheinyl moiety of coenzyme A is required for the biological activity of several proteins, including the acyl-carrier protein involved in fatty acid synthesis. *(More information)*
- Pantothenic acid is essential to all forms of life. It is ubiquitously found in foods of plant and animal origin, and dietary deficiency is very rare. *(More information)*
- The Food and Nutrition Board of the US Institute of Medicine set an adequate intake (AI) of 5 milligrams (mg)/day for adults based on the estimated daily average intake of pantothenic acid. *(More information)*
- Evidence from limited intervention studies suggests that pantothenic acid and/or pantothenol (alcohol analog) might improve the healing process of skin wounds. Yet, additional larger studies are warranted. *(More information)*
- Treatment with high-dose pantethine — a pantothenic acid derivative — has been shown to lower serum cholesterol and lipid concentrations. Although pantethine therapy appears to be well tolerated, medical supervision is indispensable. *(More information)*
- Foods rich in pantothenic acid include animal organs (liver and kidney), fish, shellfish, milk products, eggs, avocados, legumes, mushrooms, and sweet potatoes. *(More information)*
- Little or no toxicity has been associated with dietary and supplemental pantothenic acid such that no tolerable upper intake level (UL) has been set. *(More information)*

Pantothenic acid, also known as vitamin B_5, is essential to all forms of life (1). Pantothenic acid is found throughout all branches of life in the form of coenzyme A, a vital coenzyme in numerous chemical reactions (2).

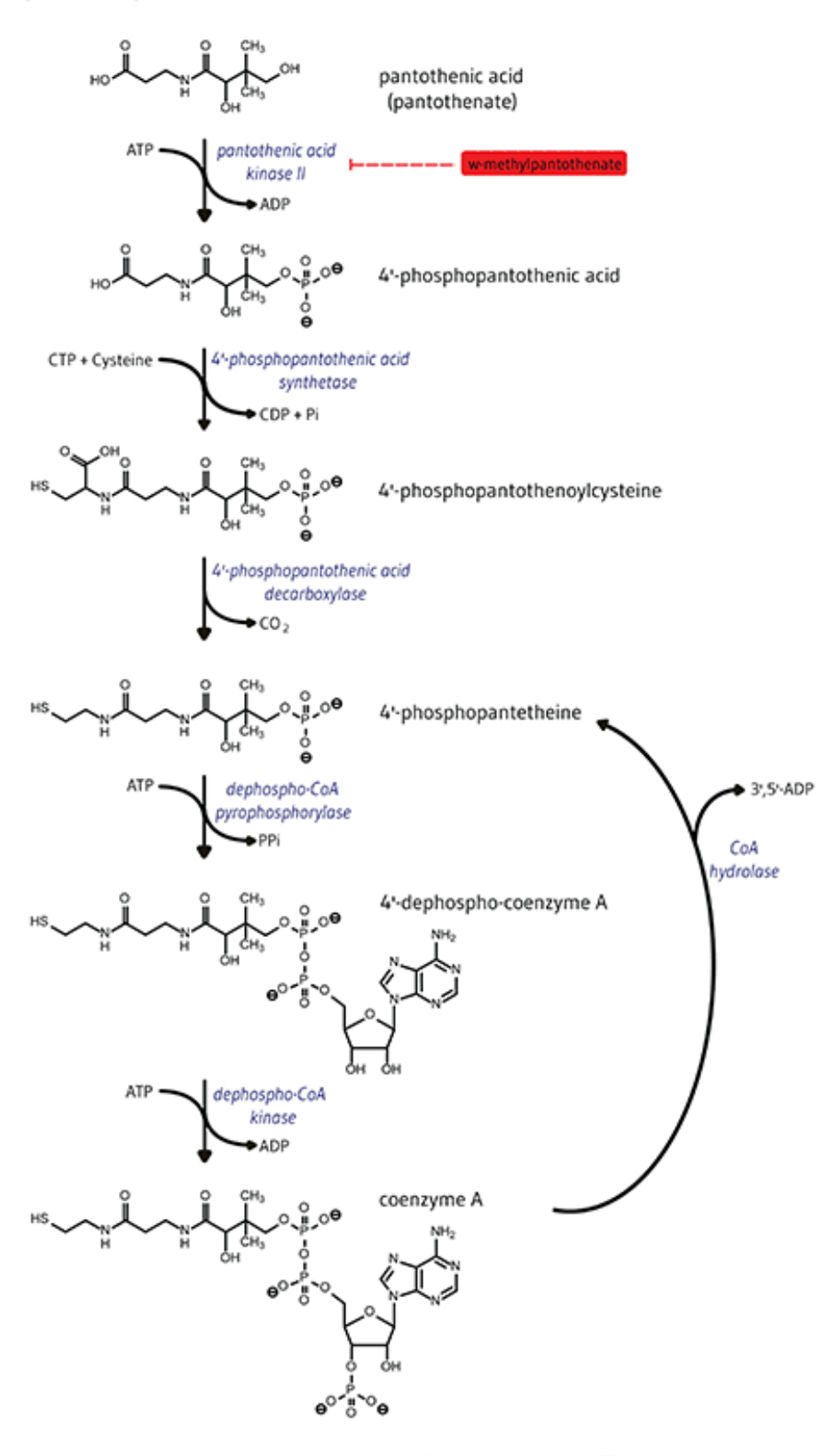
Function

Synthesis of pantothenic acid cofactors

Coenzyme A

Pantothenic acid is a precursor in the biosynthesis of coenzyme A (CoA) (**Figure 1**), an essential coenzyme in a variety of biochemical reactions that sustain life (see below). Pantothenic acid kinase II (PANKII) catalyzes the initial step of phosphorylation of pantothenic acid to 4'-phosphopantothenic acid. Coenzyme A and its derivatives inhibit the synthesis of 4'-phosphopantothenic acid, but the inhibition can be reversed by carnitine, required for the transport of fatty acids into the mitochondria (3). The subsequent reactions in this biosynthetic pathway include the synthesis of the intermediate 4'-phosphopantetheine, as well as the recycling of coenzyme A to 4'-phosphopantetheine (**Figure 1**).

Figure 1. Coenzyme A Synthesis from Pantothenic Acid


pantothenic acid (pantothenate)
ATP
pantothenic acid kinase II
ADP
ω-methylpantothenate
4'-phosphopantothenic acid
CTP + Cysteine
4'-phosphopantothenic acid synthetase
CDP + Pi
4'-phosphopantothenoylcysteine
4'-phosphopantothenic acid decarboxylase
CO2
4'-phosphopantetheine
ATP
dephospho-CoA pyrophosphorylase
PPi
3',5'-ADP
CoA hydrolase
4'-dephospho-coenzyme A
ATP
dephospho-CoA kinase
ADP
coenzyme A

Pantothenic acid is a precursor in the synthesis of coenzyme A. The initial phosphorylation reaction that converts pantothenic acid into 4'-phosphopantothenic acid is impaired in individuals with an inherited defect in the gene (*PANKII*) coding for pantothenic acid kinase II.

4'-phosphopantetheine

The 4'-phosphopantetheinyl moiety of coenzyme A can be transferred to enzymes in which 4'-phosphopantetheine is an essential cofactor for their biological activities (see 4'-phosphopantetheinylation).

Cofactor and co-substrate function

Coenzyme A

Coenzyme A reacts with acyl groups, giving rise to thioester derivatives, such as acetyl-CoA, succinyl-CoA, malonyl-CoA, and 3-hydroxy-3-methylglutaryl (HMG)-CoA. Coenzyme A and its acyl derivatives are required for reactions that generate energy from the degradation of dietary fat, carbohydrates, and proteins. In addition, coenzyme A in the form of acetyl-CoA and succinyl-CoA is involved in the citric acid cycle, in the synthesis of essential fats, cholesterol, steroid hormones, vitamins A and D, the neurotransmitter acetylcholine, and in the fatty acid β-oxidation pathway. Coenzyme A derivatives are also required for the synthesis of the hormone, melatonin, and for a component of hemoglobin called heme. Further, metabolism of a number of drugs and toxins by the liver requires coenzyme A (4).

Coenzyme A was named for its role in acetylation reactions. Most acetylated proteins in the body have been modified by the addition of an acetate group that was donated by the coenzyme A thioester derivative, acetyl-CoA. Protein acetylation alters the overall charge of proteins, modifying their three-dimensional structure and, potentially, their function. For example, acetylation is a mechanism that regulates the activity of peptide hormones, including those produced by the pituitary gland (5). Also, protein acetylation, like other posttranslational modifications, has been shown to regulate the subcellular localization, the function, and the half-life of many signaling molecules, transcription factors, and enzymes. Notably, the acetylation of histones plays a role in the regulation of gene expression by facilitating transcription (i.e., mRNA synthesis), while deacetylated histones are usually associated with chromatin compaction and gene silencing. The acetylation of histones was found to result in structural changes of the chromatin, which affect both DNA-protein and protein-protein interactions. Crosstalk between acetylation marks and other posttranscriptional modifications of the histones also facilitate the recruitment of transcriptional regulators to the promoter of genes that are subsequently transcribed (reviewed in 6).

Finally, a number of signaling molecules are modified by the attachment of long-chain fatty acids donated by coenzyme A. These modifications are known as protein acylation and have central roles in cell-signaling pathways (4).

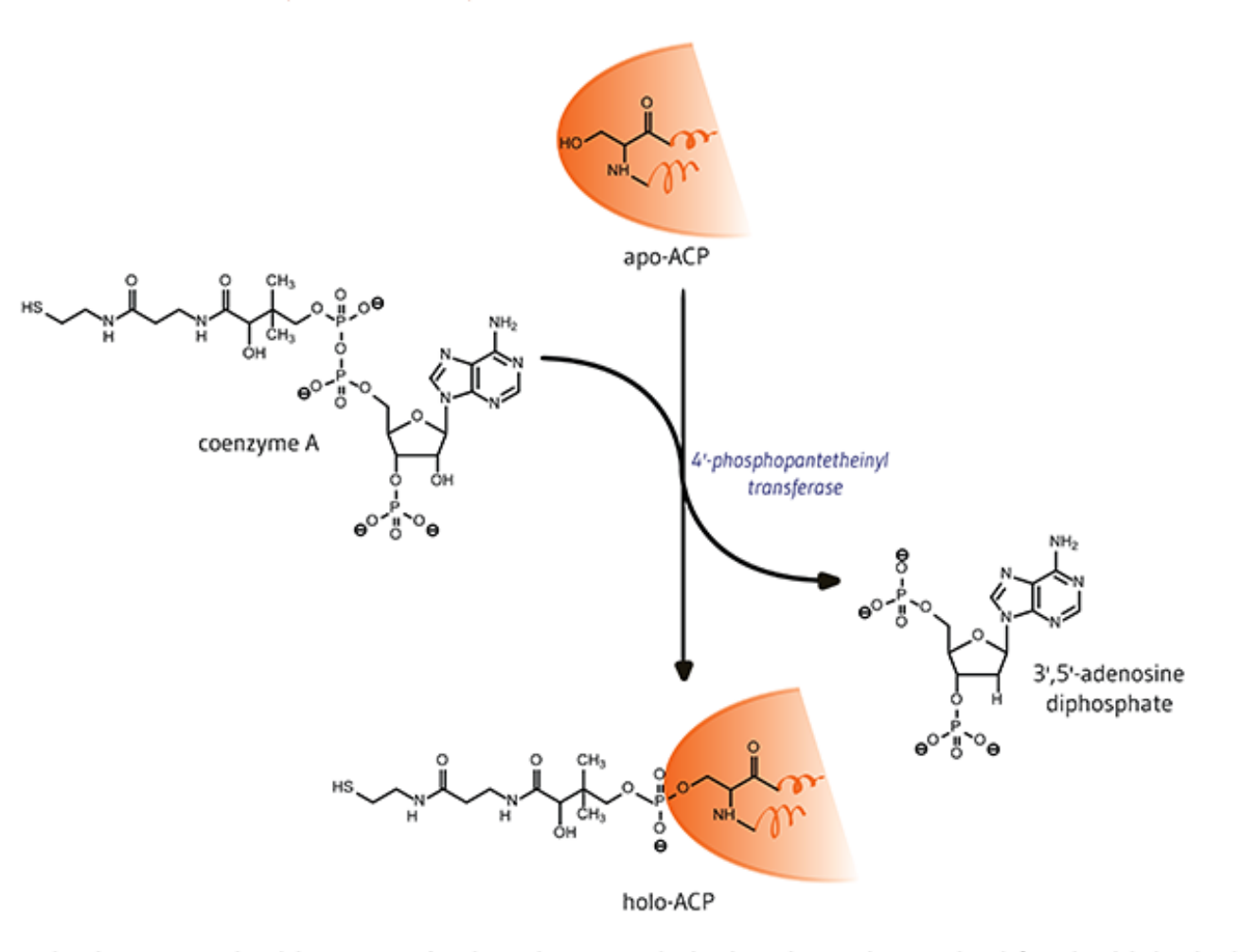
4'-phosphopantetheinylation

Specific multi-enzyme complexes, which need to carry out several reactions in an orderly manner, may require the covalent attachment of a 4'-phosphopantetheine arm to a "carrier" domain (or protein). This carrier domain holds substrates or reaction intermediates during the progression through the various enzymatic reactions. In mammals, the transfer of the 4'-phosphopantetheinyl moiety from coenzyme A to a conserved serine residue of a specific carrier domain is catalyzed by one unique phosphopantetheinyl transferase (7). The 4'-phosphopantetheinylation is necessary for the conversion of apo-enzymes into fully active holo-enzymes (see below).

Acyl-carrier protein

Lipids are fat molecules essential for normal physiological function and, among other types, include sphingolipids (essential components of the myelin sheath that enhances nerve transmission), phospholipids (important structural components of cell membranes), and fatty acids. Fatty acid synthase (FAS) is a multi-enzyme complex that catalyzes the synthesis of fatty acids. Within the FAS complex, the acyl-carrier protein (ACP) requires pantothenic acid in the form of 4'-phosphopantetheine for its activity as a carrier protein (3). A group, such as the 4'-phosphopantetheinyl moiety for ACP, is called a prosthetic group; the prosthetic group is not composed of amino acids and is a tightly bound cofactor required for the biological activity of some proteins (**Figure 2**). Acetyl-CoA, malonyl-CoA, and ACP are all required for the synthesis of fatty acids in the cytosol. During fatty acid synthesis, the acyl groups of acetyl-CoA and malonyl-CoA are transferred to the sulfhydryl group (-SH) of the 4'-phosphopantetheinyl moiety of ACP. The prosthetic group is used as a flexible arm to transfer the growing fatty acid chain to each of the enzymatic centers of the type I FAS complex. In the mitochondria, 4'-phosphopantetheine also serves as a prosthetic group for an ACP homolog present in mitochondrial type II FAS complex (8).

Figure 2. 4'-Pantetheinylation of Acyl-Carrier Protein (ACP)

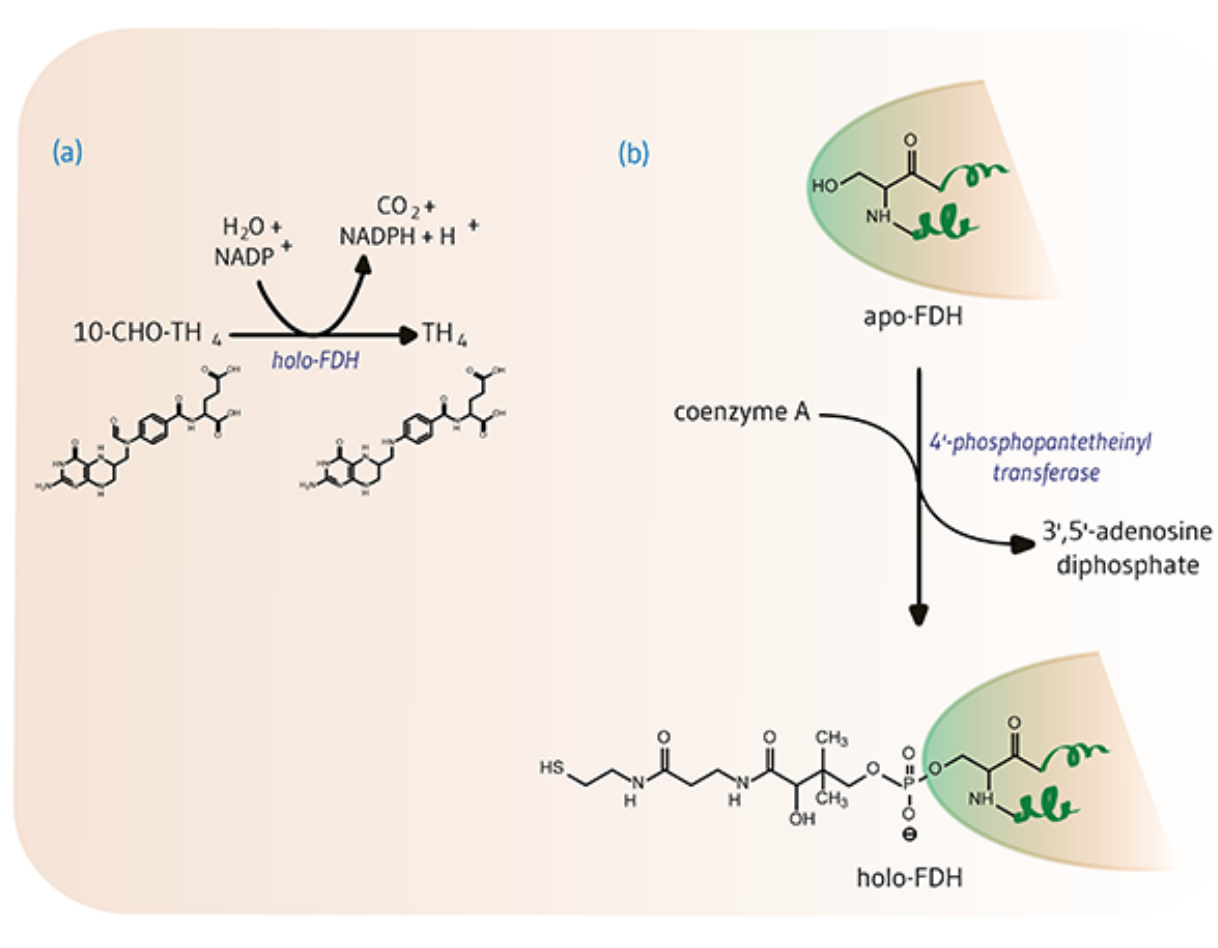

apo-ACP
coenzyme A
4'-phosphopantetheinyl transferase
3',5'-adenosine diphosphate
holo-ACP

A prosthetic group – in this case, a 4'-phosphopantetheinyl moiety – is required for the biological function of ACP. The addition of the prosthetic group occurs after ACP synthesis (post-translation) in a reaction catalyzed by 4'-phosphopantetheinyl transferase. The enzyme catalyzes the hydrolysis of coenzyme A to 3',5'-adenosine diphosphate and 4'-phosphopantetheine, and the transfer of the 4'-phosphopantetheinyl moiety to a serine residue at the active site of ACP. *ACP, acyl-carrier protein; apo-ACP, biologically inactive ACP; holo-ACP, biologically active ACP.*

10-formyltetrahydrofolate dehydrogenase

The enzyme 10-formyltetrahydrofolate dehydrogenase (FDH) catalyzes the conversion of 10-formyltetrahydrofolate to tetrahydrofolate, an essential cofactor in the metabolism of nucleic acids and amino acids (**Figure 3**). Similar to ACP, FDH requires a 4'-phosphopantetheine prosthetic group for its biological activity. The prosthetic group acts as a swinging arm to couple the activities of the two catalytic domains of FDH (9, 10). A homolog of FDH in mitochondria also requires 4'-phosphopantetheinylation to be biologically active (11).

Figure 3. 4'-Pantetheinylation of Formyltetrahydrofolate Dehydrogenase (FDH)

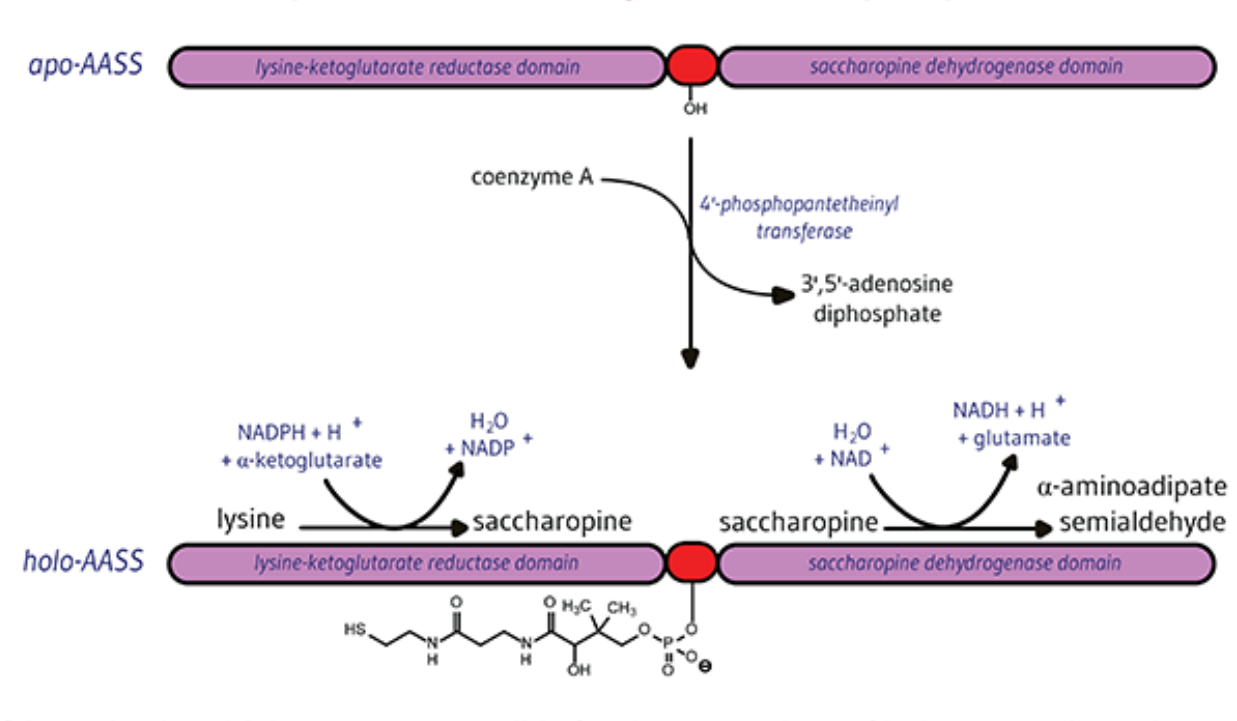


(a) The generation of TH_4 from 10-CHO-TH_4 is catalyzed by FDH, an enzyme requiring 4'-phosphopantetheine as a prosthetic group to be biologically active. Of note, 10-CHO-TH_4 can also be hydrolyzed to TH_4 (and formate) in another reaction catalyzed by formyltetrahydrofolate deformylase. (b) The enzyme 4'-phosphopantetheinyl transferase catalyzes the transfer of a 4'-phosphopantetheinyl moiety from coenzyme A to a specific serine residue of FDH, converting apo-FDH to holo-FDH. *FDH, formyltetrahydrofolate dehydrogenase; apo-FDH, biologically inactive FDH; holo-FDH, biologically active FDH; 10-CHO-TH_4, 10-formyltetrahydrofolate; TH_4, tetrahydrofolate; $NADP^+$/NADPH, nicotinamide adenine dinucleotide phosphate oxidized/reduced.*

α-Aminoadipate semialdehyde synthase

4'-phosphopantetheinylation is required for the biological activity of the apo-enzyme α-aminoadipate semialdehyde synthase (AASS). AASS catalyzes the initial reactions in the mitochondrial pathway for the degradation of lysine — an essential amino acid for humans. AASS is made of two catalytic domains. The lysine-ketoglutarate reductase domain first catalyzes the conversion of lysine to saccharopine. Saccharopine is further converted to α-aminoadipate semialdehyde in a reaction catalyzed by the saccharopine dehydrogenase domain (**Figure 4**).

Figure 4. 4'-Pantetheinylation of α-Aminoadipate Semialdehyde Synthase (AASS)


apo-AASS
lysine-ketoglutarate reductase domain
saccharopine dehydrogenase domain
OH
coenzyme A
4'-phosphopantetheinyl transferase
3',5'-adenosine diphosphate
NADPH + H^+ + α-ketoglutarate
H_2O + $NADP^+$
lysine
saccharopine
saccharopine
H_2O + NAD^+
NADH + H^+ + glutamate
α-aminoadipate semialdehyde
holo-AASS

AASS is a mitochondrial enzyme responsible for the conversions of lysine to saccharopine and saccharopine to α-aminoadipate semialdehyde in the mitochondrial pathway for lysine degradation. The first reaction is catalyzed by the lysine-ketoglutarate reductase domain of AASS, and the saccharopine dehydrogenase domain catalyzes the second reaction. Apo-AASS requires 4'-phosphopantetheine as a prosthetic group to be biologically active. The enzyme 4'-phosphopantetheinyl transferase catalyzes the transfer of a 4'-phosphopantetheinyl moiety from coenzyme A to a specific residue of AASS, converting apo-AASS to holo-AASS. The 4'-phosphopantetheinyl arm is thought to serve as a swinging arm that couples the activities of the two enzymatic domains of AASS. *AASS, α-aminoadipate semialdehyde synthase.*

Deficiency

Naturally occurring pantothenic acid deficiency in humans is very rare and has been observed only in cases of severe malnutrition. World War II prisoners in the Philippines, Burma, and Japan experienced numbness and painful burning and tingling in their feet; these symptoms were relieved specifically by pantothenic acid supplementation (4). Pantothenic acid deficiency in humans has been induced experimentally by co-administering a pantothenic acid kinase inhibitor (ω-methylpantothenate; see **Figure 1** above) and a pantothenic acid-deficient diet. Participants in this experiment complained of headache, fatigue, insomnia, intestinal disturbances, and numbness and tingling of their hands and feet (12). In another study, participants fed only a pantothenic acid-free diet did not develop clinical signs of deficiency, although some appeared listless and complained of fatigue (13).

Calcium homopantothenate (or hopantenate) is a pantothenic acid antagonist with cholinergic effects (i.e., similar to those of the neurotransmitter, acetylcholine). This compound is used in Japan to enhance mental function, especially in Alzheimer's disease. A rare side effect was the development of hepatic encephalopathy, a condition of abnormal brain function resulting from the failure of the liver to eliminate toxins. The encephalopathy was reversed by pantothenic acid supplementation, suggesting that it was due to homopantothenate-induced pantothenic acid deficiency (14). Of note, genetic mutations in the human gene *PANKII*, which codes for pantothenic acid kinase II (see **Figure 1** above), result in impaired synthesis of 4'-phosphopantetheine and coenzyme A (see Function). The disorder, called pantothenate kinase-associated neurodegeneration, is characterized by visual and intellectual impairments, dystonia, speech abnormalities, behavioral difficulties, and personality disorders (15).

Yet, because pantothenic acid is widely distributed in nature and deficiency is extremely rare in humans, most information regarding the consequences of deficiency has been gathered from experimental research in animals (reviewed in 3). Pantothenic acid-deficient rats developed damage to the adrenal glands, while monkeys developed anemia due to decreased synthesis of heme, a component of hemoglobin. Dogs with pantothenic acid deficiency developed low blood glucose, rapid breathing and heart rates, and convulsions. Chickens developed skin irritation, feather abnormalities, and spinal nerve damage associated with the degeneration of the myelin sheath. Pantothenic acid-deficient mice showed decreased exercise tolerance and diminished storage of glucose (in the form of glycogen) in muscle and liver. Mice also developed skin irritation and graying of the fur, which is reversed by pantothenic acid administration.

The diversity of symptoms emphasizes the numerous functions of pantothenic acid in its coenzyme forms.

The Adequate Intake (AI)

Because there was little information on the requirements of pantothenic acid in humans, the Food and Nutrition Board of the Institute of Medicine set an adequate intake (AI) based on observed dietary intakes in healthy population groups (**Table 1**) (16).

Table 1. Adequate Intake (AI) for Pantothenic Acid

Life Stage	Age	Males (mg/day)	Females (mg/day)
Infants	0-6 months	1.7	1.7
Infants	7-12 months	1.8	1.8
Children	1-3 years	2	2
Children	4-8 years	3	3
Children	9-13 years	4	4
Adolescents	14-18 years	5	5
Adults	19 years and older	5	5
Pregnancy	all ages	-	6
Breast-feeding	all ages	-	7

Disease Treatment

Wound healing

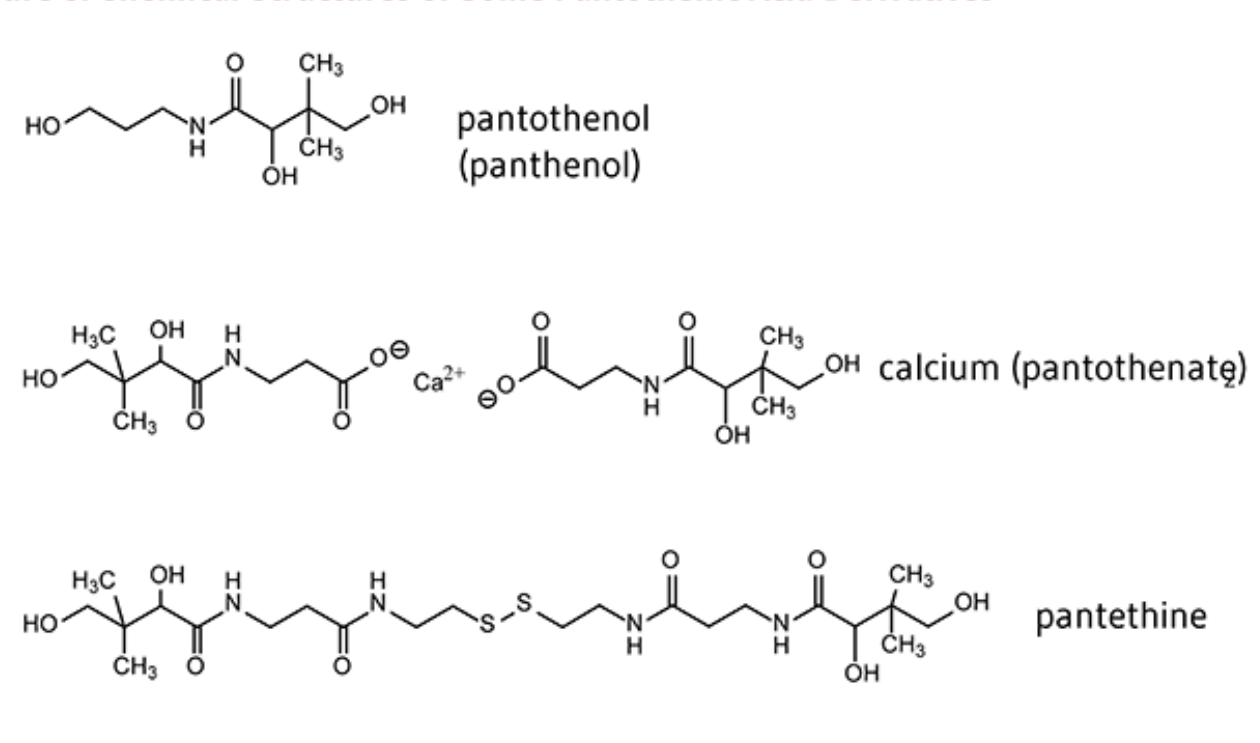
The addition of calcium D-pantothenate and/or pantothenol (**Figure 5**) to the medium of cultured skin fibroblasts given an artificial wound was found to increase cell proliferation and migration, thus accelerating wound healing *in vitro* (17, 18). Likewise, *in vitro* deficiency in pantothenic acid induced the expression of differentiation markers in proliferating skin fibroblasts and inhibited proliferation in human keratinocytes (19). The application of ointments containing either calcium D-pantothenate or pantothenol — also known as D-panthenol or dexpanthenol — to the skin has been shown to accelerate the closure of skin wounds and increase the strength of scar tissue in animals (3).

The effects of dexpanthenol on wound healing are unclear. In a placebo-controlled study that included 12 healthy volunteers, the application of dexpanthenol-containing ointment (every 12 hours for 1 to 6 days) in a model of skin wound healing was associated with an enhanced expression of markers of proliferation, inflammation, and tissue repair (20). However, the study failed to report whether these changes in response to topical dexpanthenol improved the wound-repair process compared to placebo (20). Some studies have shown no effects. Early randomized controlled trials in patients undergoing surgery for tattoo removal found that daily co-supplementation with 1 gram or 3 grams of vitamin C and 200 mg or 900 mg of pantothenic acid for 21 days did not significantly improve the wound-healing process (21, 22). Yet, in a recent randomized, double-blind, placebo-controlled study, the use of dexpanthenol pastilles (300 mg/day for up to 14 days post surgery) was found to accelerate mucosal healing after tonsillectomy in children (23).

High cholesterol

Early studies suggested that pharmacologic doses of pantethine, a pantothenic acid derivative, might have a cholesterol-lowering effect (24, 25). Pantethine is made of two molecules of pantetheine joined by a disulfide bond (chemical bond between two molecules of sulfur) (**Figure 5**). Pantethine is structurally related to coenzyme A and is found in the prosthetic group that is required for the biological function of acyl-carrier protein, formyltetrahydrofolate dehydrogenase, and α-aminoadipate semialdehyde synthase (see Function). In a 16-week, randomized, double-blind, placebo-controlled study, daily pantethine supplementation (600 mg/day for 8 weeks, followed by 900 mg/day for another 8 weeks) significantly improved the profile of lipid parameters in 120 individuals at low-to-moderate risk of cardiovascular disease (CVD). After adjusting to baseline, pantethine was found to be significantly more effective than placebo in lowering the concentrations of low-density lipoprotein-cholesterol (LDL-C) and apolipoprotein B (apoB), as well as reducing the ratio of triglycerides to high-density lipoprotein-cholesterol (TG:HDL-C) (26). Although it appears to be well tolerated and potentially beneficial in improving cholesterol metabolism, pantethine is not a vitamin, and the decision to use pharmacologic doses of pantethine to treat elevated blood cholesterol or triglycerides should only be made in collaboration with a qualified health care provider who provides appropriate follow up.

Figure 5. Chemical Structures of Some Pantothenic Acid Derivatives



Graying of hair

Mice that are deficient in pantothenic acid developed skin irritation and graying of the fur, which is reversed by pantothenic acid administration. In humans, there is no evidence that taking pantothenic acid as supplements or using shampoos containing pantothenic acid can prevent or restore hair color.

Sources

Food sources

Pantothenic acid is available in a variety of foods, usually as a component of coenzyme A (CoA) and 4'-phosphopantetheine (see **Figure 1** above). Upon ingestion, dietary coenzyme A and phosphopantetheine are hydrolyzed to pantothenic acid prior to intestinal absorption (3). Animal liver and kidney, fish, shellfish, pork, chicken, egg yolk, milk, yogurt, legumes, mushrooms, avocados, broccoli, and sweet potatoes are good sources of pantothenic acid. Whole grains are also good sources of pantothenic acid, but processing and refining grains may result in a 35 to 75% loss. Freezing and canning of foods result in similar losses (16). Large national, nutritional surveys failed to estimate pantothenic acid intake, mainly because of the scarcity of data on the pantothenic acid content of food (16). Smaller studies estimated average daily intakes of pantothenic acid to be between 4 and 7 mg/day in adults. **Table 2** lists some rich sources of pantothenic acid, along with their content in milligrams (mg). For more information on the nutrient content of foods, search USDA's FoodData Central.

Table 2. Some Food Sources of Pantothenic Acid

Food	Serving	Pantothenic Acid (mg)
Beef liver (cooked, pan fried)	3 ounces*	5.6
Sunflower seed kernels (dry roasted)	1 ounce	2.0
Fish, trout (mixed species, cooked, dry heat)	3 ounces*	1.9
Yogurt (plain, nonfat)	8 ounces	1.6
Lobster (cooked)	3 ounces	1.4
Avocado (raw, California)	½ fruit	1.0
Sweet potato (cooked, with skin)	1 medium (½ cup)	1.0
Milk	1 cup (8 fluid ounces)	0.87
Pork (tenderloin, lean, cooked, roasted)	3 ounces*	0.86
Chicken (light meat, cooked, roasted)	3 ounces*	0.83
Egg (cooked, hard-boiled)	1 large	0.70
Cheese, feta	½ cup (crumbled)	0.70
Lentils (mature seeds, cooked, boiled)	½ cup	0.63
Split peas (mature seeds, cooked, boiled)	½ cup	0.58
Mushrooms (white, raw)	½ cup (chopped)	0.52
Peanuts	1 ounce	0.50
Broccoli (cooked, boiled)	½ cup (chopped)	0.48
Orange	1 whole	0.30
Whole-wheat bread	1 slice	0.21
*A three-ounce serving of meat or fish is about the size of a deck of cards.		

Intestinal bacteria

The bacteria that normally colonize the colon (large intestine) are capable of synthesizing pantothenic acid. A specialized transporter for the uptake of biotin and pantothenic acid was identified in cultured cells derived from the lining of the colon, suggesting that humans may be able to absorb pantothenic acid and biotin produced by intestinal bacteria (27). However, the extent to which bacterial synthesis contributes to pantothenic acid intake in humans is not known (28).

Supplements

Pantothenol and pantothenate

Supplements commonly contain pantothenol (panthenol), a stable alcohol analog of pantothenic acid, which can be rapidly converted to pantothenic acid by humans. Calcium and sodium D-pantothenate, the calcium and sodium salts of pantothenic acid, are also available as supplements.

Pantethine

Pantethine is used as a cholesterol-lowering agent in Japan and is available in the US as a dietary supplement (29).

Safety

Toxicity

Pantothenic acid is not known to be toxic in humans. The only adverse effect noted was diarrhea resulting from very high intakes of 10 to 20 g/day of calcium D-pantothenate (30). However, there is one case report of life-threatening eosinophilic pleuropericardial effusion in an elderly woman who took a combination of 10 mg/day of biotin and 300 mg/day of pantothenic acid for two months (31). Due to the lack of reports of adverse effects when the Dietary Reference Intakes (DRI) for pantothenic acid were established in 1998, the Food and Nutrition Board of the Institute of Medicine did not establish a tolerable upper intake level (UL) for pantothenic acid (16). Pantethine is generally well tolerated in doses up to 1,200 mg/day. However, gastrointestinal side effects, such as nausea and heartburn, have been reported (29). Also, topical formulations containing up to 5% of dexpanthenol (D-panthenol) have been safely used for up to one month. Yet, a few cases of skin irritation, contact dermatitis, and eczema have been reported with the use of dexpanthenol-containing ointments (32, 33).

Nutrient interactions

Large doses of pantothenic acid have the potential to compete with biotin for intestinal and cellular uptake by the human sodium-dependent multivitamin transporter (hSMVT) (27, 34).

Drug interactions

Oral contraceptives (birth control pills) containing estrogen and progestin may increase the requirement for pantothenic acid (30). Use of pantethine in combination with cholesterol-lowering drugs called statins (HMG-CoA reductase inhibitors) or with nicotinic acid (see the article on Niacin) may produce additive effects on blood lipids (29).

Linus Pauling Institute Recommendation

More data are needed to define the amount of dietary pantothenic acid required to promote optimal health or prevent chronic disease. The Linus Pauling Institute supports the recommendation by the Food and Nutrition Board of 5 mg/day of pantothenic acid for adults. A varied diet should provide enough pantothenic acid for most people. Following the Linus Pauling Institute recommendation to take a daily multivitamin/mineral supplement that contains 100% of the Daily Value (DV) for pantothenic acid will ensure an intake of at least 5 mg/day.

Older adults (>50 years)

There is currently little evidence that older adults differ in their intake of or their requirement for pantothenic acid. Most multivitamin/mineral supplements provide at least 5 mg/day of pantothenic acid.

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Riboflavin

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Summary

- Riboflavin is the precursor of the coenzymes flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN). FAD and FMN act as electron carriers in a number of oxidation-reduction (redox) reactions involved in energy production, cellular antioxidant function, and in numerous metabolic pathways. *(More information)*
- Riboflavin (as FAD or FMN) is required for the metabolism of iron and vitamin B_6, and in the synthesis of niacin from tryptophan. It also plays an essential role in folate and related one-carbon metabolism, where FAD is required as a cofactor for methylenetetrahydrofolate reductase (MTHFR), a key folate-metabolizing enzyme. *(More information)*
- Clinical signs of riboflavin deficiency include skin disorders, angular stomatitis, cheilosis, glossitis, and corneal vascularization. Riboflavin deficiency occurs commonly in low- and middle-income countries. *(More information)*
- Subclinical deficiency (low status) of riboflavin without clinical signs may be widespread, including in high-income countries, but it usually goes undetected because riboflavin biomarkers are very rarely measured in human studies. *(More information)*
- Low riboflavin status is associated with preeclampsia in pregnant women, a condition that may progress to eclampsia and cause severe bleeding and death *(More information)*. It is also linked with cataracts in older individuals. *(More information)*
- Deficient/low status of riboflavin interferes with the metabolism of folate, particularly in individuals with the variant 677TT genotype in *MTHFR*. There is some evidence that these individuals exhibit a higher risk of cancer. *(More information)*
- Case reports have shown that patients with autosomal recessive disorders of riboflavin metabolism may benefit from riboflavin supplementation. *(More information)*
- The *MTHFR* C677T polymorphism is associated with an increased risk of hypertension. Intervention studies have shown that supplementation with riboflavin (the MTHFR cofactor) effectively lowers blood pressure, specifically in individuals with the variant *MTHFR* 677TT genotype. *(More information)*
- Riboflavin supplementation has been evaluated as a prophylactic agent for migraine headache, but the results are conflicting. *(More information)*
- Riboflavin supplementation has been studied as a potential adjunct therapy in cancer, certain eye disorders, and multiple sclerosis. *(More information)*

Riboflavin is a water-soluble B vitamin, also known as vitamin B_2. Riboflavin is primarily found as an integral component of the coenzymes flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN) (1). Coenzymes derived from riboflavin are termed flavocoenzymes, and enzymes that use a flavocoenzyme are called flavoproteins (2).

Function

Oxidation-reduction (redox) reactions

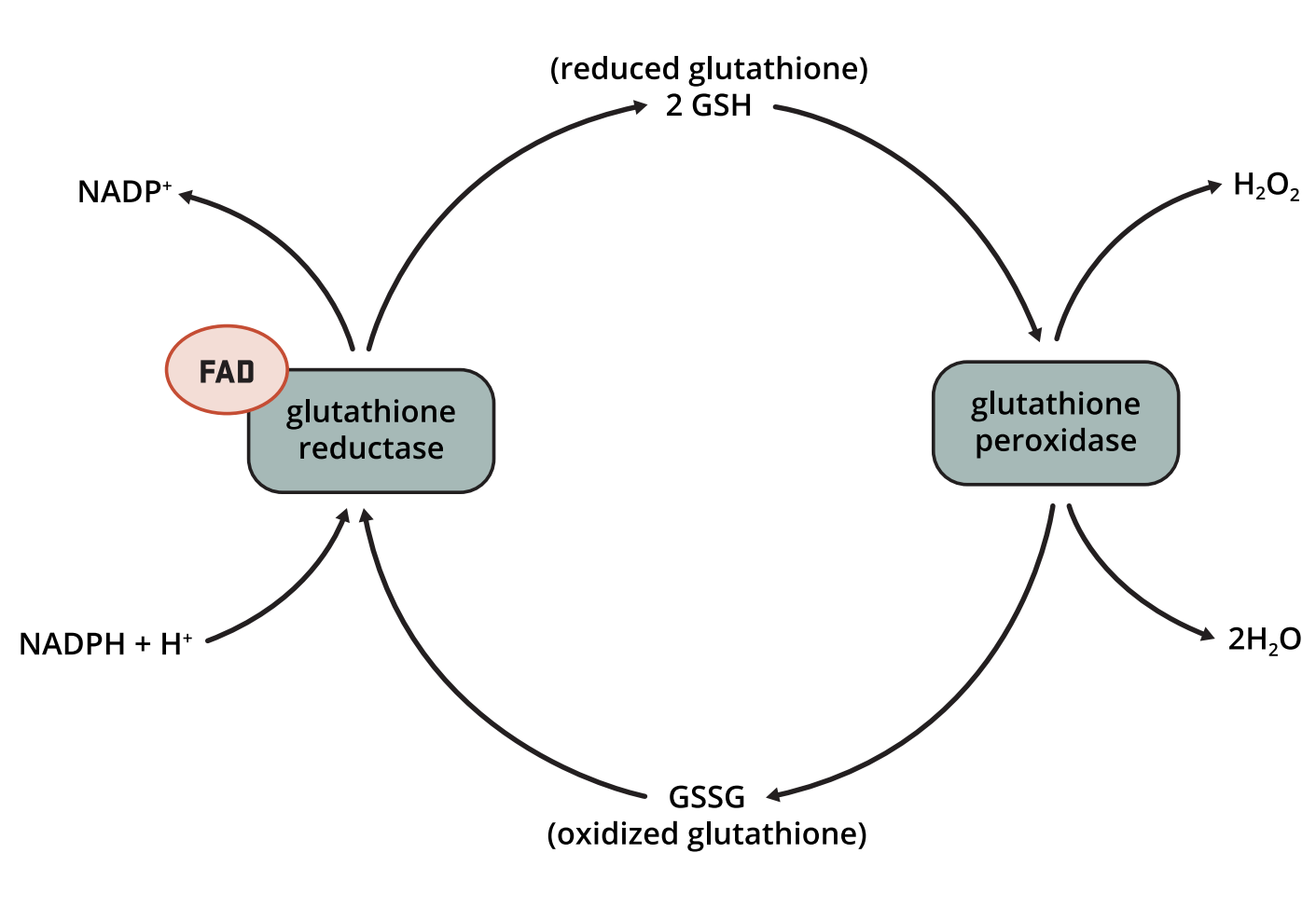
Living organisms derive most of their energy from redox reactions, which are processes that involve the transfer of electrons. Flavocoenzymes participate in redox reactions in numerous metabolic pathways (3). They are critical for the metabolism of carbohydrates, lipids, and proteins. FAD is part of the electron transport (respiratory) chain, which is central to energy production. In conjunction with cytochrome P-450, flavocoenzymes also participate in the metabolism of drugs and toxins (4).

Antioxidant functions

Glutathione reductase is a FAD-dependent enzyme that participates in the redox cycle of glutathione. The glutathione redox cycle plays a major role in protecting organisms from reactive oxygen species, such as hydroperoxides. Glutathione reductase requires FAD to regenerate two molecules of reduced glutathione from oxidized glutathione. Riboflavin deficiency has been associated with increased oxidative stress (4) Measurement of glutathione reductase activity in red blood cells is commonly used to assess riboflavin nutritional status (5).

Glutathione peroxidases (GPx), selenium-containing enzymes, require two molecules of reduced glutathione to break down hydroperoxides. GPx are involved in the glutathione oxidation-reduction (redox) cycle (**Figure 1**).

Figure 1. Glutathione Oxidation-Reduction (Redox) Cycle



FAD - flavin adenine dinucleotide (one of the two cofactor forms of riboflavin)

One molecule of hydrogen peroxide is reduced to two molecules of water, while two molecules of glutathione (GSH) are oxidized in a reaction catalyzed by the selenoenzyme, glutathione peroxidase. Oxidized glutathione (GSSG) may be reduced by the flavin adenine dinucleotide (FAD)-dependent enzyme, glutathione reductase.

Xanthine oxidase, another FAD-dependent enzyme, catalyzes the oxidation of hypoxanthine and xanthine to uric acid. Uric acid is one of the most effective water-soluble antioxidants in the blood. Riboflavin deficiency can result in decreased xanthine oxidase activity, reducing blood uric acid levels (6).

Nutrient interactions

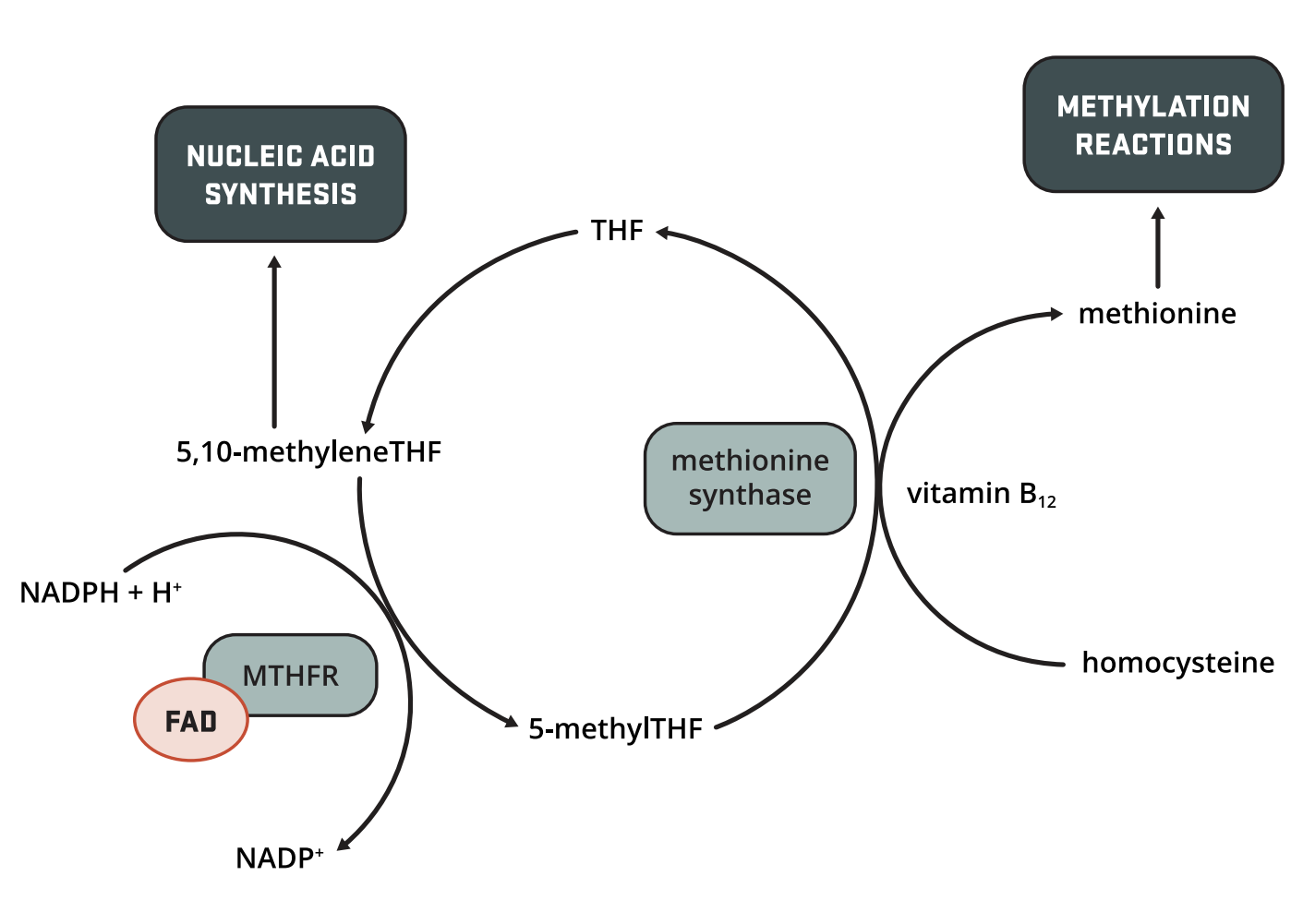
Riboflavin (as FAD or FMN) is required for the synthesis of niacin from tryptophan, and in the metabolism of vitamin B_6 and iron. It is also essential for folate and related one-carbon metabolism, where FAD is required as a cofactor for methylenetetrahydrofolate reductase (MTHFR), a key folate-metabolizing enzyme.

B-complex vitamins

Flavoproteins are involved in the metabolism of several other vitamins: vitamin B_6, niacin, vitamin B_{12}, and folate. Therefore, low and deficient riboflavin status can affect several enzyme systems. The conversion of vitamin B_6 to its active coenzyme form in tissues, pyridoxal 5'-phosphate (PLP), requires the FMN-dependent enzyme, pyridoxine 5'-phosphate oxidase (PPO) (7). Human studies have provided evidence of the metabolic dependency of vitamin B_6 on riboflavin status in older (8-10) and younger (10) adults. The synthesis of the niacin-containing coenzymes, NAD and NADP, from the amino acid tryptophan, requires the FAD-dependent enzyme, kynurenine 3-monooxygenase. Severe riboflavin deficiency can thus decrease the conversion of tryptophan to NAD and NADP, increasing the risk of niacin deficiency (3).

Methylenetetrahydrofolate reductase (MTHFR) is an FAD-dependent enzyme that plays a key role in one-carbon metabolism by catalyzing the reduction of 5,10 methyleneTHF to 5 methylTHF. Once formed, 5 methylTHF is used by methionine synthase for the vitamin B_{12}-dependent conversion of homocysteine to methionine and the formation of THF (**Figure 2**). Both FMN and FAD are coenzymes for the enzyme methionine synthase reductase, which is responsible for the regeneration of methylcobalamin, the biologically active form of vitamin B_{12} acting as a coenzyme for methionine synthase (11). Along with other B vitamins (folate, vitamin B_{12}, and vitamin B_6), higher dietary riboflavin intakes have been associated with lower plasma concentrations of homocysteine (12). In individuals homozygous for the C677T polymorphism in the *MTHFR* gene, low riboflavin status is associated with elevated plasma homocysteine, and in turn linked with a higher risk of cardiovascular disease and other chronic diseases (13, 14). Furthermore, supplementation with riboflavin results in marked lowering of homocysteine concentrations specifically in individuals with the variant *MTHFR* 677TT genotype (15). Such results illustrate that chronic disease risk may be influenced by complex interactions between genetic and dietary factors.

Figure 2. Folate and Nucleic Acid Metabolism



FAD - flavin adenine dinucleotide (one of two cofactor forms of riboflavin)
MTHFR - methylenetetrahydrofolate reductase
THF - tetrahydrofolate

5,10-methyleneTHF is required for the synthesis of nucleic acids, and 5-methylTHF is required for the formation of methionine from homocysteine. Methionine, in the form of S-adenosylmethionine, is required for many methylation reactions, including DNA methylation. MTHFR is a flavin-dependent enzyme required to catalyze the reduction of 5,10-methyleneTHF to 5-methylTHF.

Iron

Riboflavin deficiency alters iron metabolism. Although the mechanism is not clear, research in animals suggests that riboflavin deficiency may impair iron absorption, increase intestinal loss of iron, and/or impair iron utilization for the synthesis of hemoglobin (16). In humans, low dietary intake of riboflavin has been associated with an increased risk for anemia (17), and improving riboflavin nutritional status has been found to increase circulating hemoglobin levels (18). Correction of riboflavin deficiency in individuals who are both riboflavin and iron deficient improves the response of iron-deficiency anemia to iron therapy (19). Anemia during pregnancy, a worldwide public health problem, is responsible for considerable perinatal morbidity and mortality (20, 21). The management of maternal anemia typically involves supplementation with iron alone or iron in combination with folic acid (22). It is possible that the inclusion of riboflavin could enhance the effects of iron-folic acid supplementation in treating maternal anemia, but the evidence is limited. There are, however, randomized, double-blind intervention trials conducted in pregnant women with anemia in Southeast Asia showing that a combination of folic acid, iron, vitamin A, and riboflavin improved hemoglobin levels and decreased anemia prevalence compared to iron-folic acid supplementation alone (23, 24).

Deficiency

Ariboflavinosis is the medical name for clinical riboflavin deficiency, which occurs commonly in low- and middle-income countries. Riboflavin deficiency is rarely found in isolation; it typically occurs in combination with deficiencies of other water-soluble vitamins. Clinical signs of riboflavin deficiency include sore throat, redness and swelling of the lining of the mouth and throat, cracks or sores on the outsides of the lips (cheliosis) and at the corners of the mouth (angular stomatitis), inflammation and redness of the tongue (magenta tongue), and a moist, scaly skin inflammation (seborrheic dermatitis). Other signs may involve the formation of blood vessels in the clear covering of the eye (vascularization of the cornea) and decreased red blood cell count in which the existing red blood cells contain normal levels of hemoglobin and are of normal size (normochromic normocytic anemia) (1, 3). Subclinical deficiency (low status) of riboflavin without clinical signs may be widespread, including in high-income countries, but usually goes undetected because riboflavin biomarkers are very rarely measured in human studies. Low or deficient riboflavin status may result in decreased conversion of vitamin B_6 to its active coenzyme form (PLP) and decreased conversion of tryptophan to niacin (see Nutrient interactions).

Preeclampsia is defined as the presence of elevated blood pressure, protein in the urine, and edema (significant swelling) during pregnancy. About 5% of women with preeclampsia progress to eclampsia, a significant cause of maternal and fetal death. Eclampsia is characterized by seizures, in addition to high blood pressure and increased risk of hemorrhage (severe bleeding) (25). A study in 154 pregnant women at increased risk of preeclampsia found that those who were riboflavin deficient were 4.7 times more likely to develop preeclampsia than those who had adequate riboflavin nutritional status (26). The cause of preeclampsia-eclampsia is not known. Decreased intracellular levels of flavocoenzymes could cause mitochondrial dysfunction, increase oxidative stress, and interfere with nitric oxide release and thus blood vessel dilation – all of these changes have been associated with preeclampsia (26).

A 2015 meta-analysis of 54 case-control studies found that the *MTHFR* C677T polymorphism was associated with an increased risk of preeclampsia, especially in Caucasian and Asian populations (27). The reduction in the flavoprotein MTHFR activity observed in individuals with the variant *MTHFR* 677TT genotype leads to an increase in plasma homocysteine (14); higher homocysteine concentrations have been associated with preeclampsia (28). One small randomized controlled trial in 450 pregnant women in West Africa, without specified *MTHFR* genotype but at high risk for preeclampsia, found that supplementation with 15 mg of riboflavin daily was not effective in preventing the condition (29), but the study was likely underpowered to detect a significant effect. Further studies are needed to assess the potential benefit of riboflavin supplementation in reducing perinatal complications generally and specifically in preeclamptic women with the *MTHFR* 677TT genotype.

Risk factors for riboflavin deficiency

Alcoholics are at an increased risk of riboflavin deficiency, likely due to decreased dietary intake, decreased absorption, and/or impaired utilization of riboflavin. Interestingly, the elevated blood homocysteine concentrations associated with riboflavin deficiency rapidly decline during alcohol withdrawal (30). Additionally, people with anorexia rarely consume adequate dietary riboflavin, and those who are lactose intolerant are unlikely to meet requirements due to the avoidance of dairy products, the major dietary sources of riboflavin. The conversion of riboflavin into the active cofactor forms FAD and FMN is impaired in hypothyroidism and adrenal insufficiency (3, 4). Further, people who are very active physically (athletes, laborers) may have slightly increased riboflavin requirements. However, riboflavin supplementation has not generally been found to increase exercise tolerance or performance (31) unless the individual was riboflavin deficient (32).

individuals are riboflavin deficient (32).

The Recommended Dietary Allowance (RDA)

The RDA for riboflavin, revised in 1998, is based on the prevention of deficiency (**Table 1**). Clinical signs of deficiency in humans appear at intakes of less than 0.5 to 0.6 milligrams (mg)/day, and urinary excretion of riboflavin is seen at intake levels of approximately 1 mg/day (1).

Table 1. Recommended Dietary Allowance (RDA) for Riboflavin

Life Stage	Age	Males (mg/day)	Females (mg/day)
Infants	0-6 months	0.3 (AI)	0.3 (AI)
Infants	7-12 months	0.4 (AI)	0.4 (AI)
Children	1-3 years	0.5	0.5
Children	4-8 years	0.6	0.6
Children	9-13 years	0.9	0.9
Adolescents	14-18 years	1.3	1.0
Adults	19 years and older	1.3	1.1
Pregnancy	all ages	-	1.4
Breast-feeding	all ages	-	1.6

Disease Prevention

Cataracts

Age-related cataracts are the leading cause of visual disability in the US and other developed countries. Research has focused on the role of nutritional antioxidants because of evidence that light-induced oxidative damage of lens proteins may lead to the development of age-related cataracts. A case-control study found significantly decreased risk of age-related cataracts (33% to 51%) in men and women in the highest quintile of dietary riboflavin intake (median of 1.6 to 2.2 mg/day) compared to those in the lowest quintile (median of 0.08 mg/day in both men and women) (33). Another case-control study reported that individuals in the highest quintile of riboflavin status, as measured by red blood cell glutathione reductase activity, had approximately one-half the occurrence of age-related cataract as those in the lowest quintile of riboflavin status, though the results were not statistically significant (34). A cross-sectional study of 2,900 Australian men and women, 49 years of age and older, found that those in the highest quintile of riboflavin intake were 50% less likely to have cataracts than those in the lowest quintile (35). A prospective cohort study of more than 50,000 women did not observe a difference between rates of cataract extraction between women in the highest quintile of riboflavin intake (median of 1.5 mg/day) and women in the lowest quintile (median of 1.2 mg/day) (36). However, the range between the highest and lowest quintiles was small, and median intake levels for both quintiles were above the RDA for riboflavin. A study in 408 women found that higher dietary intakes of riboflavin were inversely associated with a five-year change in lens opacification (37). A randomized controlled trial using a fractional factorial design showed that compared with placebo, the combined supplementation with riboflavin (3 mg/day) and niacin (40 mg/day) for five to six years reduced the prevalence of nuclear cataract but increased the progression of posterior subcapsular cataracts in population affected by multiple nutrient deficiency living in rural China (38). Of note is that the results of this trial are somewhat conflicting, and the study design does not allow the effects of riboflavin and niacin to be differentiated. In summary, there is some evidence predominantly from observational studies, that suggests higher riboflavin status might be beneficial; however, more evidence from well-designed, randomized controlled trials is needed to confirm a role for riboflavin in the prevention of cataracts.

Cancer

The flavoprotein, methylenetetrahydrofolate reductase (MTHFR), plays a pivotal role in folate-mediated one-carbon metabolism. MTHFR converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the cofactor form necessary for the re-methylation of homocysteine to methionine (see **Figure 2** above). The conversion of homocysteine to methionine is of importance for homocysteine detoxification and for the production of S-adenosylmethionine (SAM), the methyl donor for the methylation of DNA and histones. Folate deficiency and elevated homocysteine concentrations may increase cancer risk (see the article on Folate). Aberrant methylation changes are also known to alter the structure and function of DNA and histones during cancer development (39). Since MTHFR controls the detoxification of homocysteine and the supply of methyl groups for SAM synthesis, a reduction in its activity can affect homocysteine metabolism and disturb cellular methylation processes. The substitution of a cytosine by a thymine in position 677 (c.677C>T) in the *MTHFR* gene is a polymorphism that affects the binding of FAD and leads to an increased propensity for MTHFR to lose its flavin coenzyme (40). Subjects homozygous for this mutation (*MTHFR* 677TT genotype) exhibit reduced MTHFR activity and increased risk for a wide variety of cancers (41-43), but the evidence of an association between this polymorphism and cancer is inconsistent, with some reports suggesting a reduction in colorectal cancer risk with the T allele (44).

As mentioned above (see B-complex vitamins), riboflavin intake is a determinant of homocysteine concentration. This suggests that riboflavin status can influence MTHFR activity and the metabolism of folate, thereby affecting cancer risk (43). In a randomized, double-blind, placebo-controlled study, 93 subjects with colorectal polyps and 86 healthy subjects were given a placebo, folic acid (400 or 1,200 μg/day), or folic acid (400 μg/day) plus riboflavin (5 mg/day) for 45 days. These interventions significantly improved folate and riboflavin status in vitamin-supplemented individuals compared to those taking the placebo. Interestingly, riboflavin enhanced the effect of 400 μg folic acid on circulating 5-methyltetrahydrofolate (5-MTHF) specifically in the polyp patients with the C677T genetic variant (45). This suggests that riboflavin may improve the response to folic acid supplementation in individuals with a reduced MTHFR activity. Additionally, a prospective cohort study of 88,045 postmenopausal women found total (dietary plus supplemental) intake of riboflavin to be inversely correlated with colorectal cancer risk when comparing the highest (>3.97 mg) and lowest (<1.80 mg) quartiles of daily intake (46); intake in the reference group was well above the RDA for riboflavin of 1.1 mg/day. The subjects in this study were not prescreened to identify those with the variant *MTHFR* 677TT genotype, and the association between this polymorphism and colorectal cancer remains unclear, with some reports suggesting a reduction in cancer risk with the T allele (44). Two meta-analyses have found inverse associations between riboflavin intake and risk of colorectal cancer (47, 48). The most recent of these was a dose-response meta-analysis that pooled results from five prospective cohort studies, nine case-control studies, and two studies reporting blood concentrations of riboflavin. This analysis found that higher intakes of riboflavin were associated with a significantly lower risk of colorectal cancer (RR=0.87; 95% CI, 0.81-0.93); inverse associations were observed for both dietary riboflavin intake and total daily intake from the diet and supplements (48).

Associations between riboflavin intake and cancer risk have also been evaluated in other types of cancer. A seven-year intervention study evaluated the use of riboflavin-fortified salt in 22,093 individuals at high risk for esophageal cancer in China. Riboflavin status and esophageal pathology (percent normal, dysplastic, and cancerous tissues) improved in the intervention group compared to the control group, but the lower incidence of esophageal cancer found in the intervention group was not statistically significant (49). Additionally, a 25-year follow up of an intervention trial in patients at high risk for gastric cancer found that dietary supplementation with riboflavin (3.2 mg/day) and niacin (40 mg/day) for five years decreased the risk of mortality from esophageal cancer by 8% but had no effect on mortality from gastric cancer (50). In the Melbourne Collaborative Cohort Study, which followed 41,514 men and women over a 15-year period, weak inverse associations were found between riboflavin intake and lung cancer (51) and breast cancer (52); no association of riboflavin intake with prostate cancer was observed in this cohort (53). A 2017 meta-analysis of 10 observational studies found an overall inverse association of riboflavin intake and breast cancer incidence and reported a 6% lower risk with each 1 mg/day increment of riboflavin intake (54). Further, studies to date have not found riboflavin intake or measures of riboflavin status to be associated with renal cell carcinoma, as reviewed in a recent meta-analysis (55).

Disease Treatment

Migraine headaches

Some evidence indicates that impaired mitochondrial oxygen metabolism in the brain may play a role in the pathology of migraine headaches. Since riboflavin is the precursor of the two flavocoenzymes (FAD and FMN) required by the flavoproteins of the mitochondrial electron transport chain, supplemental riboflavin has been investigated as a treatment for migraine. A randomized controlled trial examined the effect of very high dose riboflavin (400 mg/day) for three months on migraine prevention in 54 men and women with a history of recurrent migraine headaches (56). Riboflavin compared to placebo reduced attack frequency and the number of headache days, though the beneficial effect was most pronounced during the third month of treatment (56). Another study by the same investigators found that treatment with either a β-blocker drug or high-dose riboflavin (400 mg/day) for four months resulted in clinical improvement, but each therapy appeared to act on a distinct pathological mechanism: β-blockers on abnormal cortical information processing and riboflavin on decreased brain mitochondrial energy reserve (57). A small study in 23 patients reported a reduction in median migraine attack frequency after supplementation with 400 mg of riboflavin daily for three months (58). A single-blinded, randomized, parallel group trial in 85 patients with migraine headaches (ages 15-55 years), high-dose riboflavin supplementation (400 mg/day) for 12 weeks decreased migraine frequency, duration, and severity compared to baseline and was as effective as sodium valproate (500 mg/day) (59), a medication with established efficacy in migraine preventative therapy (60). Riboflavin elicited significantly fewer adverse effects compared to the drug (59). Thus, although the available trials have been small and short term, most studies to date suggest that high-dose riboflavin supplementation might be a useful adjunct therapy in adults with migraine headaches.

A few randomized controlled trials have investigated the effect of riboflavin supplementation on the frequency and severity of headache attacks in children with migraines. An initial study evaluated riboflavin at 200 mg/day for 12 weeks in 48 children of ages 5 to 15 years old (61). A second study was a cross-over trial with half of the 42 children, ages 6 to 13, receiving 50 mg/day riboflavin for 16 weeks then placebo (100 mg/day carotene) for 16 weeks (with a four-week washout period in between each), while the other half were first given the placebo then riboflavin (62). Neither study showed differences in the frequency, duration, or intensity of migraines between treatments. However, a more recent trial found a benefit of intervention with higher dose riboflavin: children with migraine treated with 400 mg/day of riboflavin for 12 weeks (n=30) had reductions in migraine frequency and duration, but not intensity, compared to placebo (n=30), yet no benefit was seen in children taking 200 mg/day for 12 weeks in this study (63). Additionally, a randomized controlled trial in 98 adolescents, ages 12 to 19 years, found that 400 mg/day of riboflavin for three months decreased both headache frequency and duration and improved migraine-related disability compared to placebo (64). Retrospective studies of children and adolescents suffering from migraine have also suggested some benefit associated with supplemental riboflavin (65-67). Thus, studies to date are somewhat conflicting, and more research is needed to understand whether riboflavin supplementation might have utility in the treatment of childhood migraine and the most effective dose required for any beneficial effects.

Metabolic disorders

Increasing evidence from case reports indicates that patients with autosomal recessive disorders caused by defective FAD-dependent enzymes could benefit from riboflavin supplementation.

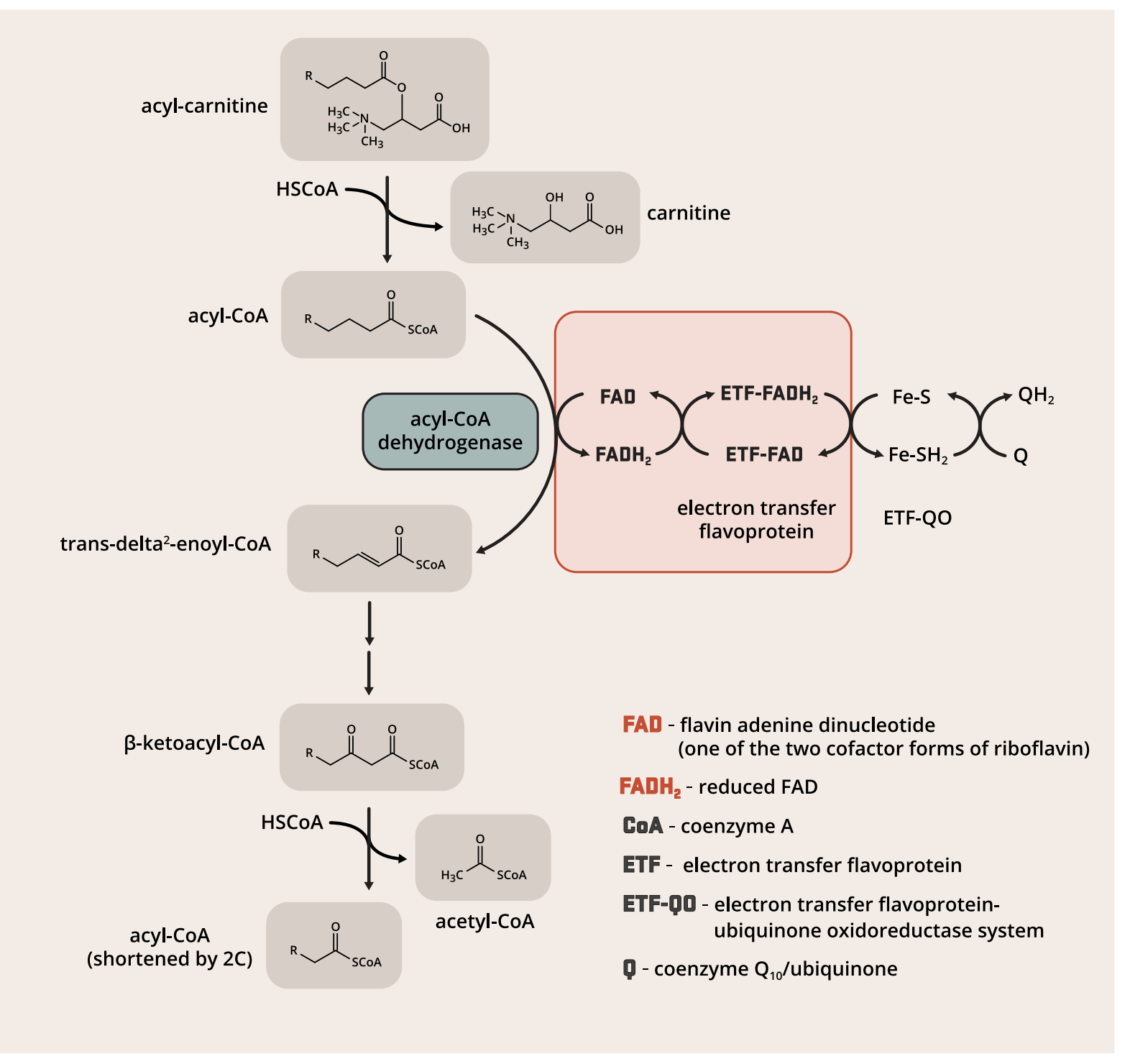
Multiple acyl-CoA dehydrogenase deficiency (MADD)

MADD, also known as type II glutaric aciduria (or acidemia), is a fatty acid metabolism disorder characterized by the accumulation of short-, medium-, and long-chain acyl-carnitines in various tissues. MADD is classified into three separate types based on age of onset and clinical symptoms: type I MADD is evident in the neonatal period and is characterized by the presence of congenital anomalies; type II MADD is present in the neonatal period but lacks congenital defects; and type III is characterized by late onset, from infancy through adulthood (68), and even as late as the seventh decade of life (69). Clinical symptoms of type I and II MADD present shortly after birth and include hypoglycemia, hyperammonemia, metabolic acidosis, hepatomegaly, and respiratory distress (68, 70); these forms of MADD are often fatal in infancy, even if treated. Type III MADD usually presents later in life and includes milder symptoms, varying from periodic vomiting, rhabdomyolysis, muscle pain and weakness, and exercise intolerance (68, 70). Peripheral neuropathy has also recently been reported as a symptom of adult-onset MADD (71).

MADD is caused by autosomal recessive mutations in genes that impair the activity of enzymes involved in the transfer of electrons from acyl-coenzyme A (acyl-CoA) to coenzyme Q_{10}/ubiquinone inside the mitochondria (**Figure 3**). *ETFA*, *ETFB*, and *ETFDH* code for the two subunits of the electron transfer flavoprotein (ETF-A and -B) and for ETF dehydrogenase/ubiquinone oxidoreductase (ETFDH/ETFQO), respectively. Deficiencies in these enzymes (ETF or ETFDH) lead to a decrease in oxidized FAD, which becomes unavailable for FAD-dependent dehydrogenation reactions, including the first step in β-oxidation – a major fatty acid catabolic process that takes place in the mitochondria. A defect in fatty acid β-oxidation causes lipid accumulation in skeletal muscles, leading to lipid storage myopathy characterized by muscle pain and weakness and exercise intolerance.

Together with a low-fat, high-carbohydrate diet, riboflavin supplementation has led to significant clinical improvements in patients with *ETFDH* mutations. The specific type of the mutation in *ETF*/*ETFDH* contributes to age of onset, severity, and responsiveness to riboflavin treatment (70, 72). Additionally, the report of a 20-year-old man with riboflavin-responsive MADD failed to find mutations in *ETF* and *ETFDH* genes, suggesting that other sites of mutation should not be excluded (73). Finally, secondary deficiencies in the respiratory chain are observed in MADD and appear to respond favorably to riboflavin supplementation (72, 74).

Figure 3. Fatty Acid β-Oxidation and the Electron Transfer Flavoprotein System


acyl-carnitine
HSCoA
carnitine
acyl-CoA
acyl-CoA dehydrogenase
FAD
ETF-FADH₂
Fe-S
QH₂
FADH₂
ETF-FAD
Fe-SH₂
Q
electron transfer flavoprotein
ETF-QO
trans-delta²-enoyl-CoA
β-ketoacyl-CoA
HSCoA
acetyl-CoA
acyl-CoA (shortened by 2C)
FAD - flavin adenine dinucleotide (one of the two cofactor forms of riboflavin)
FADH₂ - reduced FAD
CoA - coenzyme A
ETF - electron transfer flavoprotein
ETF-QO - electron transfer flavoprotein-ubiquinone oxidoreductase system
Q - coenzyme Q₁₀/ubiquinone

Multiple Acyl-CoA Dehydrogenase Deficiency (MADD) is caused by mutations in the genes coding for the ETF and the ETF-QO. These flavoproteins are essential for electron transfer from the fatty acid β-oxidation pathway to the respiratory chain.

Acyl-CoA dehydrogenase 9 deficiency (ACAD9)

Acyl-CoA dehydrogenase family member 9 (ACAD9) is an FAD-dependent enzyme with important roles in both the electron transport chain and β-oxidation of fatty acids in the mitochondria. Recessive mutations in the *ACAD9* gene coding for ACAD9 have been found in patients with mitochondrial complex I deficiency, a respiratory chain disorder (75). Complex I carries electrons from NADH to coenzyme Q_{10} in the electron transport chain. Defective oxidative phosphorylation (ATP synthesis by the respiratory chain) due to complex I deficiency has been linked to a broad variety of clinical manifestations, from neonatal death to late-onset neurodegenerative diseases. The clinical symptoms of complex I deficiency due to *ACAD9* mutations typically include muscle weakness, exercise intolerance, lactic acidosis, and hypertrophic cardiomyopathy (76). However, symptoms can be of varying severity, likely due to the remaining functional activity of ACAD9. For example, affected patients have been reported to exhibit a spectrum of cardiac deficits, including isolated, mild ventricular hypertrophy to severe hypertrophic cardiomyopathy (77).

Riboflavin supplementation (100-300 mg/day) has been shown to increase complex I activity in patients with childhood-onset clinical forms of ACAD9 deficiency. Improvements in muscle strength and exercise tolerance have also been associated with riboflavin supplementation (78-80). A review of cases of ACAD9 deficiency presenting in infancy (i.e., cases with severe symptoms) found riboflavin treatment to be associated with improved survival: 7 of 22 patients treated with riboflavin succumbed to the illness compared to 16 out of 17 untreated patients (76).

Defective riboflavin transport-associated disorders

SLC52A1, *SLC52A2*, and *SLC52A3* genes code for the human riboflavin transporters RFVT1, RFVT2, and RFVT3, respectively. Mutations in these genes lead to riboflavin transporter deficiency, a rare neurodegenerative condition with variable age of onset, from infancy to early stages of adulthood. Autosomal recessive mutations in *SLC52A2* or *SLC52A3* respectively cause disorders known as riboflavin transporter deficiency type 2 (RFVT2 deficiency) and riboflavin transporter deficiency type 3 (RFVT3 deficiency). These genetic disorders were formerly called Brown-Vialetto-Van Laere syndrome and Fazio-Londe syndrome (81). Riboflavin transporter deficiency caused by mutation of *SLC52A1* is exceedingly rare and has been reported in only three cases (reviewed in 82).

Clinical features of riboflavin transporter deficiency can include muscle weakness in the arms and legs, sensory ataxia, bulbar palsy with hypotonia and facial weakness, sensorineural deafness, and respiratory insufficiency (83, 84). High-dose, oral supplementation with riboflavin improves many of these symptoms in the majority of affected patients; such treatment should be given at the time of suspected riboflavin transporter deficiency for a better prognosis (84). A 2016 review of the published literature found that oral supplementation with riboflavin – at doses ranging from 7 to 60 mg/kg/day – led to improved symptoms in 71% of the patients (n=39) and to no deaths (83). In contrast, all of the untreated patients (n=31) had a progression of the disease and a mortality rate of at least 48% (83).

Riboflavin-responsive trimethylaminuria

Primary trimethylaminuria is caused by defective oxidation of trimethylamine by a liver flavoprotein called flavin containing mono-oxygenase 3 (FMO3). Individuals with FMO3 deficiency have increased levels of trimethylamine in urine, sweat, and breath (85). This socially distressing condition is known as "fish odor syndrome" due to the fishy odor and volatile nature of trimethylamine. *FMO3* gene mutations are usually associated with mild or intermittent trimethylaminuria; the condition is sometimes limited to peri-menstrual periods in female subjects or to the consumption of trimethylamine-rich food. The clinical management of the condition includes dietary restriction of trimethylamine and its precursors, such as foods rich in choline and seafood, as well as cruciferous vegetables that contain both trimethylamine precursors and FMO3 antagonists (86). The use of riboflavin supplements was reported in a 17-year-old female patient affected by pyridoxine non-responsive homocystinuria (87). The disease was initially treated with betaine (a choline derivative), which caused body odor secondary to FMO3 deficiency. Riboflavin supplementation (200 mg/day) reduced trimethylamine excretion and the betaine treatment-related body odor. Similar effects were seen with riboflavin supplementation in two pediatric patients (88). The data suggest that riboflavin might help maximize residual FMO3 enzyme activity in patients with primary trimethylaminuria. Moreover, a recent case report in a 35-year-old male with HIV described supplemental riboflavin as an effective treatment for secondary trimethylaminuria caused by antiretroviral therapy (89).

Hypertension

Hypertension in adulthood is recognized as the leading risk factor contributing to mortality worldwide primarily from cardiovascular disease, while hypertension in pregnancy leads to serious adverse fetal and maternal outcomes. A number of risk factors are recognized to contribute to the development of hypertension. In recent years, evidence has emerged from genetic and clinical studies pointing to the role of one-carbon metabolism in blood pressure (90). The common *MTHFR* C677T polymorphism, affecting 1 in 10 adults globally, is associated with higher blood pressure, although this is much less well recognized compared with the phenotype of elevated homocysteine concentrations that was established at the time of discovery of this polymorphism and its link with cardiovascular disease (91). Meta-analyses show that this polymorphism is associated with an increased risk of hypertension by up to 87% and of heart disease and stroke by up to 40% (92). The *MTHFR* C677T polymorphism is also associated with a significantly higher risk of hypertension in pregnancy (93) and with preeclampsia (27).

Since FAD is required as a cofactor for the MTHFR enzyme and the *MTHFR* C677T polymorphism results in decreased MTHFR activity, studies have investigated whether affected individuals may benefit from riboflavin supplementation. In an initial randomized controlled trial in 77 healthy young adults stratified by *MTHFR* genotype, riboflavin supplementation at dietary levels (1.6 mg/day for 12 weeks) resulted in marked lowering of homocysteine concentrations in the *MTHFR* 677TT genotype group, but not in the 677CC or 677CT genotype groups who exhibited normal plasma homocysteine at baseline (15). Three randomized controlled trials subsequently investigated the effect of riboflavin on blood pressure in patients with hypertension with or without overt cardiovascular disease (91, 94, 95). The results of these trials showed that supplementation with low-dose riboflavin (1.6 mg/day for 16 weeks) resulted in significant lowering of blood pressure and reduction in incidence of hypertension specifically in those patients with the variant *MTHFR* 677TT genotype. Riboflavin intervention reduced mean systolic/diastolic blood pressure in those with the TT genotype from 144/87 to 131/80 mm Hg, with no response observed in those without the genetic variant (i.e., the CT or CC genotypes) (89). Notably, the 13 mm Hg decrease in systolic blood pressure occurred even though over 80% of the patients were taking one or more antihypertensive drugs at recruitment, and the addition of supplemental riboflavin was shown to greatly enhance the achievement of goal blood pressure with routine antihypertensive drugs (89, 91). Furthermore, the magnitude of blood pressure response achieved with riboflavin in these trials compares very favorably with typical decreases from other interventions, such as dietary salt reductions of 3 g/day (3.6/1.9 mm Hg) and 6 g/day (7.1/3.9 mm Hg). The trial findings therefore suggest that the excess risk of hypertension linked to this genetic polymorphism can be overcome by low-dose riboflavin supplementation. Also, analysis of plasma samples from individuals participating in these trials showed lower concentrations of S-adenosylmethionine (SAM), an important methyl group donor for methylation reactions, in those with the *MTHFR* 677TT genotype versus the CC genotype (96). However, riboflavin supplementation (1.6 mg/day) for 12 weeks was shown to increase plasma concentrations of SAM and another one-carbon metabolite, cystathionine (96), and thus may have potential in correcting the altered one-carbon metabolism arising with the variant TT genotype.

Thus, studies to date indicate that riboflavin supplementation may have benefits in lowering blood pressure and reducing hypertension in individuals (and sub-populations) affected by the common *MTHFR* C677T polymorphism. However, the mechanisms explaining the blood pressure phenotype and its responsiveness to riboflavin remain unclear. Future studies examining the effects of riboflavin supplementation on one-carbon metabolism may help to elucidate the biological mechanisms involved. Interestingly, a recent randomized controlled trial found that riboflavin supplementation in those with the variant *MTHFR* 677TT genotype resulted in altered DNA methylation of certain genes known to be involved in blood pressure regulation (97).

Cancer

Anticancer agents often display various side effects that may force patients to limit the dose or to discontinue the treatment. The antioxidant effect of co-administering riboflavin (10 mg/day), niacin (50 mg/day), and coenzyme Q_{10} (100 mg/day) was evaluated in 78 postmenopausal patients with breast cancer treated with tamoxifen for 90 days. This supplementation effectively prevented the oxidative stress associated with tamoxifen treatment (98).

Riboflavin can also act as a photosensitizer, and this property may have value in photodynamic therapy of cancer. A mouse model was used to assess the effect of riboflavin in combination with cisplatin, one of the most effective anticancer agents. Under light exposure, riboflavin administration reduced cisplatin-induced DNA damage in the liver and kidneys (99). These results are promising, but human studies are needed to examine whether riboflavin is an effective adjunct to chemotherapy.

Corneal disorders

Corneal ectasia is an eye condition characterized by irregularities of the cornea that affect vision. Corneal cross-linking – a fairly new procedure used by professionals to limit the progression of corneal damage –involves the use of topical riboflavin in conjunction with ultraviolet-A irradiation. Riboflavin functions as a photosensitizer in the reaction. Cross-linking modifies the properties of the cornea and strengthens its architecture (100, 101).

Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune disease of unknown etiology that is characterized by the progressive destruction of myelin and nerve fibers in the central nervous system, causing neurological symptoms in affected individuals (102). Riboflavin appears to have a role in the formation of myelin (103), and oxidative stress has been implicated in the pathogenesis of MS; thus, riboflavin may be helpful in treatment of the disease. A strong inverse association between dietary riboflavin intake and risk for MS was initially observed in a case-control study (104). In a mouse model of MS (i.e., experimental autoimmune encephalomyelitis), riboflavin supplementation improved clinical measures of the disease (105). However, a randomized, double-blind, placebo-controlled pilot study in 29 patients with MS found that supplementation with 10 mg/day of riboflavin for six months had no effect on MS-related disability, assessed by the Expanded Disability Status Scale (106). Large-scale randomized, placebo-controlled trials are needed to determine whether riboflavin supplementation has a beneficial effect in the treatment of MS.

Sources

Food sources

Most plant- and animal-derived foods contain at least small quantities of riboflavin. In the US, wheat flour and bread have been enriched with riboflavin (as well as thiamin, niacin, and iron) since 1943. Data from a US national survey indicate that the average dietary intake of riboflavin is 2.5 mg/day for men and 1.8 mg/day for women (107); these intakes are well above the RDA values of 1.3 mg/day for men and 1.1 mg/day for women. Surveys of adults of ages 70 years or older showed similar intakes: 2.2 mg/day for older men and 1.8 mg day for older women (107).

Riboflavin is heat-stable, but it is easily destroyed upon exposure to light. For instance, up to 50% of the riboflavin in milk contained in a clear glass bottle can be destroyed after two hours of exposure to bright sunlight (6). Nationally representative surveys from the US, Ireland, and the UK showed that milk and other dairy products were the main dietary contributors to riboflavin intake, followed by meat and ready-to-eat breakfast cereals (108-110). Some foods with substantial amounts of riboflavin are listed in **Table 2**, along with their riboflavin content in milligrams (mg). For more information on the nutrient content of food, search USDA's FoodData Central.

The bioavailability of riboflavin from food is reported to be very high, nearly 95% (108). Limited data exist for the relative bioavailability of riboflavin from different food sources, however a cross-over study in healthy women using stable isotopes and kinetic modeling did not find significant differences in riboflavin absorption from milk and spinach (111).

Table 2. Some Food Sources of Riboflavin

Food	Serving	Riboflavin (mg)
Fortified breakfast wheat, puffed cereal	1 cup	0.22
Milk (low-fat, 1%)	1 cup	0.42
Cheddar cheese	1 ounce	0.12
Egg (cooked, hard-boiled)	1 large	0.26
Almonds, unsalted	1 ounce	0.33
Salmon (chinook, cooked)	3 ounces*	0.13
Halibut (greenland, cooked, dry-heat)	3 ounces	0.09
Chicken, light meat (roasted)	3 ounces	0.09
Chicken, dark meat (roasted)	3 ounces	0.16
Beef (ground, cooked)	3 ounces	0.16
Broccoli (boiled, chopped)	½ cup	0.10
Asparagus (boiled)	½ cup	0.13
Spinach (boiled)	½ cup	0.21
Bread, whole-wheat	1 slice	0.05
Bread, white (enriched)	1 slice	0.07

*A three-ounce serving of meat is about the size of a deck of cards.

Supplements

The most common forms of riboflavin available in supplements are riboflavin and riboflavin 5'-monophosphate. Riboflavin is commonly found in multivitamin and vitamin B-complex preparations (112).

Safety

Toxicity

No toxic or adverse effects of high riboflavin intake in humans are known. Studies in cell culture indicate that excess riboflavin may increase the risk of DNA strand breaks in the presence of chromium (VI), a known carcinogen (113). This may be of concern to workers exposed to chrome, yet no data in humans are available. High-dose riboflavin therapy has been found to intensify urine color to a bright yellow (flavinuria), but this is a harmless side effect. The Food and Nutrition Board did not establish a tolerable upper intake level (UL) when the RDA was revised in 1998 (1).

Drug interactions

Several early reports indicated that women taking high-dose oral contraceptives had diminished riboflavin biomarker status. However, when investigators controlled for dietary riboflavin intake, no differences between users of oral contraceptives and non-users were found (1). Phenothiazine derivatives like the anti-psychotic medication, chlorpromazine (Thorazine), and tricyclic antidepressants inhibit the conversion of riboflavin to FAD and FMN, as do the anti-malarial medication, quinacrine, and the cancer chemotherapy agent, adriamycin (4). Long-term use of the anticonvulsant, phenobarbital, may increase destruction of riboflavin by liver enzymes, increasing the risk of deficiency (3). Additionally, chronic alcohol consumption has been associated with riboflavin deficiency. In rats chronically fed alcohol, the inhibition of riboflavin transporters caused impairment in intestinal absorption and renal re-uptake of the vitamin (114).

Linus Pauling Institute Recommendation

The RDA for riboflavin (1.3 mg/day for men and 1.1 mg/day for women), which should prevent deficiency in most individuals, is easily met by eating a varied diet. Consuming a varied diet should supply 1.5 mg to 2 mg of riboflavin a day. Following the Linus Pauling Institute recommendation to take a multivitamin/mineral supplement containing 100% of the Daily Values (DV) will ensure an intake of at least 1.3 mg/day of riboflavin.

Older adults (>50 years)

Some experts in nutrition and aging feel that the RDA (1.3 mg/day for men and 1.1 mg/day for women) leaves little margin for error in people over 50 years of age (115, 116). A study of independently living people between 65 and 90 years of age found that almost 25% consumed less than the recommended riboflavin intake, and 10% had biochemical evidence of deficiency (117). Epidemiological studies of cataract prevalence indicate that riboflavin intakes of 1.6 to 2.2 mg/day may reduce the risk of developing age-related cataracts. Additionally, older people suffering from acute ischemic stroke were found to be deficient for riboflavin (118), and riboflavin deficiency has been linked to a higher risk of fracture in postmenopausal women with the *MTHFR* 677T variant (119). Individuals whose diets may not supply adequate riboflavin, especially those over 50 years of age, should consider taking a multivitamin/mineral supplement, which generally provides at least 1.3 mg/day of riboflavin.

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Thiamin

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Summary

- Thiamin pyrophosphate (TPP), the active form of thiamin, is involved in several enzyme functions associated with the metabolism of carbohydrates, branched-chain amino acids, and fatty acids. *(More information)*
- Severe thiamin deficiency leads to beriberi, a disease that affects multiple organ systems, including the central and peripheral nervous systems. *(More information)*
- Wernicke's encephalopathy refers to an acute neurologic disorder secondary to thiamin deficiency. The Wernicke-Korsakoff syndrome results in persistent alterations in memory formation, along with the encephalopathy-related symptoms. *(More information)*
- Thiamin deficiency can result from poor dietary intake, inadequate provision in parenteral nutrition, reduced gastrointestinal absorption, increased metabolic requirements, or excessive loss of thiamin. Chronic alcohol consumption is the primary cause of thiamin deficiency in industrialized countries. *(More information)*
- Alteration in glucose metabolism has been associated with decreased plasma thiamin concentrations in patients with diabetes. Correction of thiamin deficiency may reduce the risk of vascular complications in these patients. *(More information)*
- Alzheimer's disease has been associated with altered glucose metabolism and thiamin deficiency. Although some promising results have been observed in animal models, it is not known whether supplementation with thiamin or benfotiamine (a synthetic precursor of thiamin) might slow the cognitive decline in patients with Alzheimer's disease. *(More information)*
- A recent study found decreased levels of thiamin in the brain of patients with Huntington's disease. Clinical trials are needed to evaluate whether vitamin supplementation might be a potential therapy. *(More information)*
- Diuretic-induced thiamin excretion may increase the risk of thiamin deficiency and disease severity in subjects with congestive heart failure. Further studies are needed to assess the inclusion of thiamin supplementation in the management of this disease. *(More information)*
- Intravenous thiamin has been studied as potential treatment for sepsis, either as a monotherapy or in combination with other agents like vitamin C and corticosteroids. Large-scale clinical trials are needed to determine its efficacy. *(More information)*

Thiamin (also spelled thiamine) is a water-soluble B vitamin, also known as vitamin B_1 or aneurine (1). Isolated and characterized in the 1930s, thiamin was one of the first organic compounds to be recognized as a vitamin (2). Thiamin occurs in the human body as free thiamin and as various phosphorylated forms: thiamin monophosphate (TMP), thiamin triphosphate, adenosine thiamin triphosphate, and thiamin pyrophosphate (TPP), which is also known as thiamin diphosphate.

Function

Coenzyme function

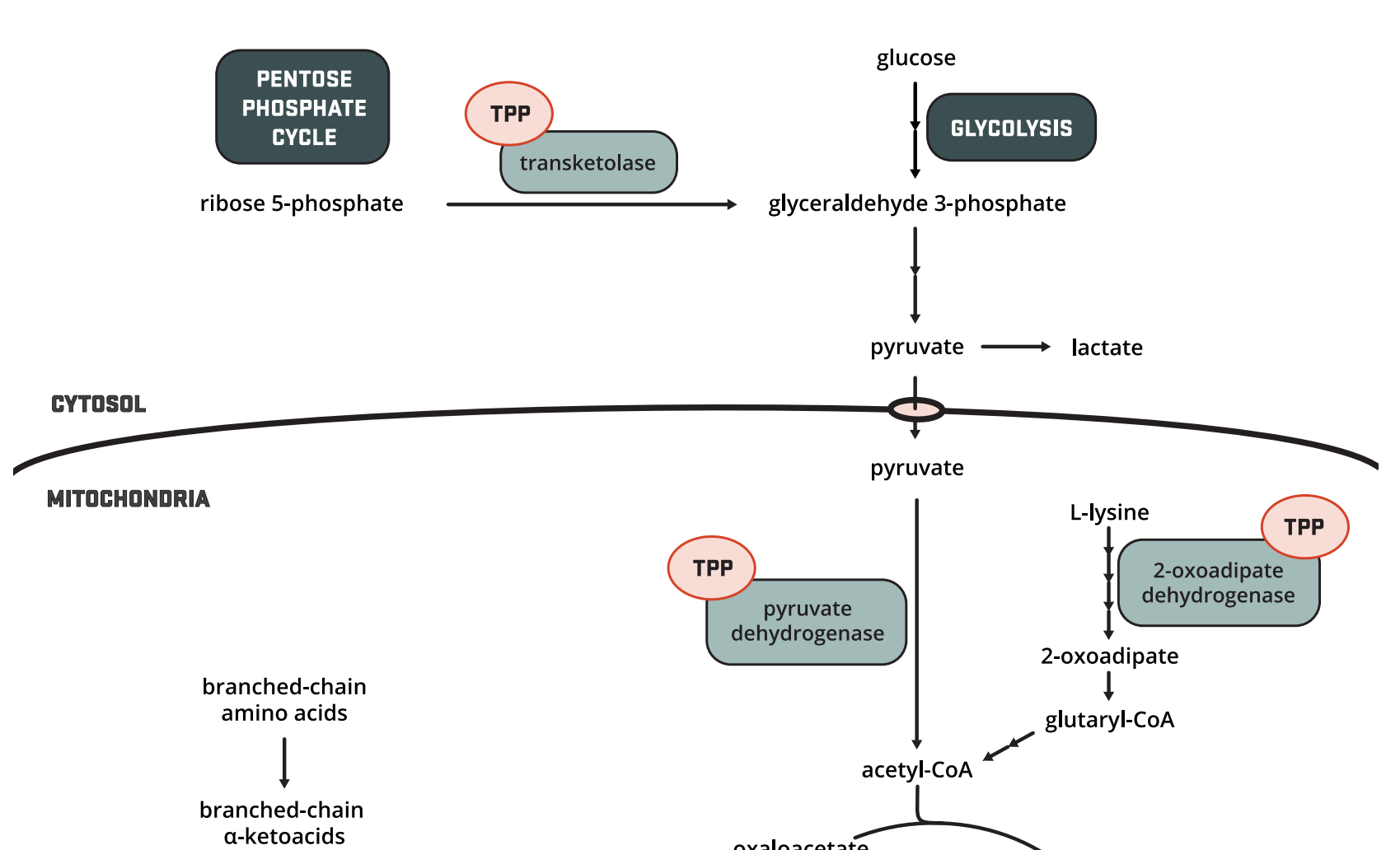
The synthesis of TPP from free thiamin requires magnesium, adenosine triphosphate (ATP), and the enzyme, thiamin pyrophosphokinase. In humans, TPP is required as a coenzyme in the metabolism of carbohydrates and branched-chain amino acids. Forms of thiamin are also needed for ribose synthesis and for α-oxidation of 3-methyl-branched fatty acids.

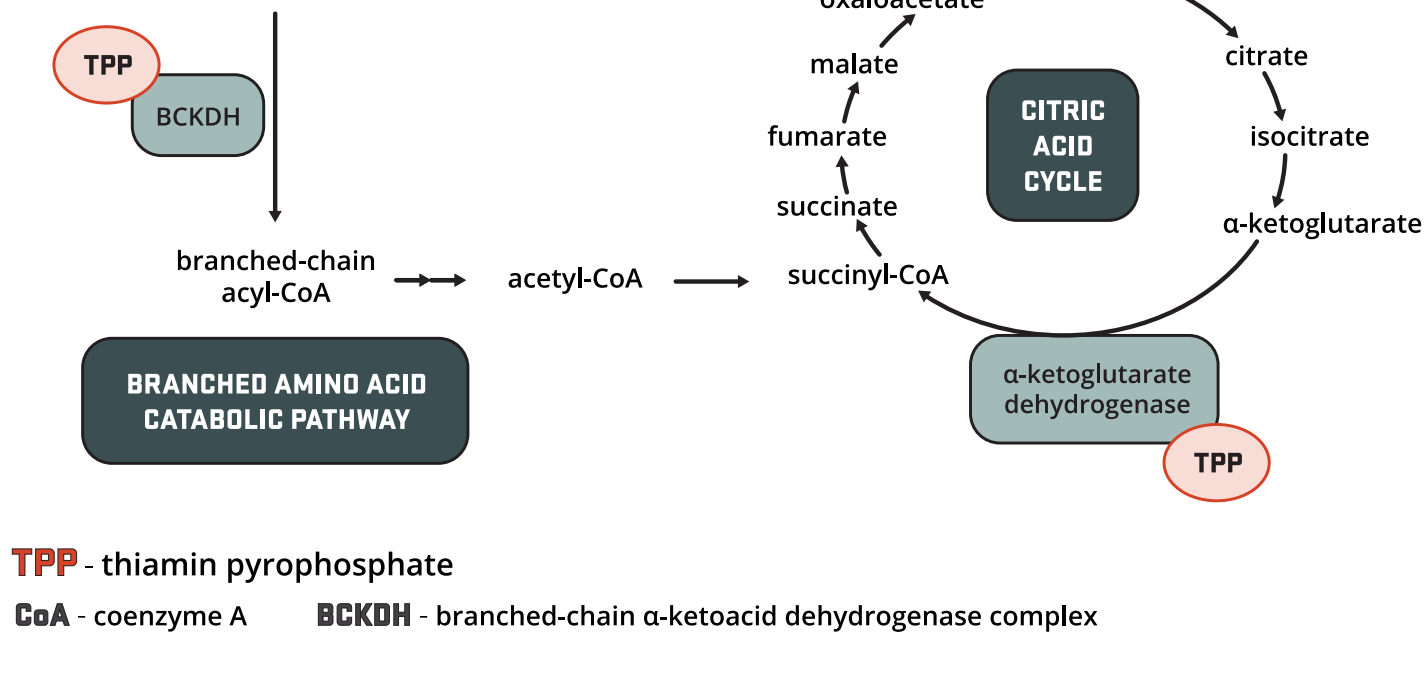
Pyruvate dehydrogenase, **α-ketoglutarate dehydrogenase**, **2-oxoadipate dehydrogenase**, and **branched-chain α-ketoacid dehydrogenase (BCKDH)** each comprise a different enzyme complex found within cellular organelles called mitochondria. They catalyze the decarboxylation of pyruvate, α-ketoglutarate, 2-oxoadipate, and branched-chain amino acids (BCAA) to form acetyl-coenzyme A (CoA), succinyl-CoA, glutaryl-CoA, and derivatives of BCAA, respectively (**Figure 1**). All products play critical roles in the production of energy from food through their connection to the citric acid (Krebs) cycle (2). BCAA, including leucine, isoleucine, and valine, are eventually degraded into acetyl-CoA and succinyl-CoA to fuel the citric acid cycle. The catabolism of the three BCAAs also contributes to the production of cholesterol and donates nitrogen for the synthesis of the neurotransmitters, glutamate and g-aminobutyric acid (GABA) (3). In addition to the thiamin coenzyme (TPP), each dehydrogenase complex requires a niacin-containing coenzyme (NAD), a riboflavin-containing coenzyme (FAD), and lipoic acid.

Transketolase catalyzes critical reactions in another metabolic pathway occurring in the cytosol, known as the pentose phosphate pathway. One of the most important intermediates of this pathway is ribose-5-phosphate, a phosphorylated 5-carbon sugar required for the synthesis of the high-energy ribonucleotides, such as ATP and guanosine triphosphate (GTP). Nucleotides are the building blocks of nucleic acids, DNA, and RNA. The pentose phosphate pathway also supplies various anabolic pathways, including fatty acid synthesis, with the niacin-containing coenzyme NADPH (1, 4). Because transketolase decreases early in thiamin deficiency and, unlike most thiamin-dependent enzymes, is present in red blood cells, measurement of its activity in red blood cells has been used to assess thiamin nutritional status (2, 5, 6).

2-Hydroxyacyl-CoA lyase is a TPP-dependent enzyme in peroxisomes that catalyzes the catabolism of 3-methyl-branched fatty acids through the process of α-oxidation, the oxidative removal of a single carbon atom from fatty acids like phytanic acid (7).

Figure 1. Metabolic Pathways Requiring Thiamin Pyrophosphate (TPP)





Deficiency

Beriberi, the disease resulting from severe thiamin deficiency, was described in Chinese literature as early as 2600 B.C. Thiamin deficiency affects the cardiovascular, muscular, gastrointestinal, and central and peripheral nervous systems (2). Beriberi has been subdivided into dry, wet, cerebral, or gastrointestinal, depending on the systems affected by severe thiamin deficiency (1, 8).

Dry beriberi

The main feature of dry (paralytic or nervous) beriberi is peripheral neuropathy. Early in the course of the neuropathy, "burning feet syndrome" may occur. Other symptoms include abnormal (exaggerated) reflexes, as well as diminished sensation and weakness in the legs and arms. Muscle pain and tenderness and difficulty rising from a squatting position have also been observed (9).

Wet beriberi

In addition to neurologic symptoms, wet (cardiac) beriberi is characterized by cardiovascular manifestations of thiamin deficiency, which include rapid heart rate, enlargement of the heart, severe swelling (edema), difficulty breathing, and ultimately, congestive heart failure. The Japanese literature describes the acute fulminant form of wet beriberi as “shoshin” (10).

Cerebral beriberi

Cerebral beriberi may lead to Wernicke's encephalopathy and Korsakoff's psychosis, especially in people who abuse alcohol. The diagnosis of Wernicke's encephalopathy is based on a "triad" of signs, which include abnormal eye movements, stance and gait ataxia, and cognitive impairment. Due in part to an overlap of symptoms with alcoholic delirium, Wernicke’s encephalopathy is thought to be underdiagnosed (11). If left untreated, the irreversible neurologic damage can cause additional clinical manifestations known as Korsakoff’s psychosis. This syndrome – also called Korsakoff’s dementia, Korsakoff's amnesia, or amnestic confabulatory syndrome – involves a confused, apathetic state and a profound memory disorder, with severe amnesia and loss of recent and working memory.

Thiamin deficiency affecting the central nervous system is referred to as Wernicke's disease when the amnesic state is not present and Wernicke-Korsakoff syndrome (WKS) when the amnesic symptoms are present along with the eye-movement and gait disorders. Rarer neurologic manifestations can include seizures (12). Most WKS sufferers are alcoholics, although it has been observed in other disorders of gross malnutrition, including stomach cancer and AIDS. Administration of intravenous thiamin to WKS patients generally results in prompt improvement of the eye symptoms, but improvements in motor coordination and memory may be less, depending on how long the symptoms have been present. Evidence of increased immune cell activation and increased free radical production in the areas of the brain that are selectively damaged suggests that oxidative stress plays an important role in the neurologic pathology of thiamin deficiency (13).

Gastrointestinal beriberi

TPP is critical for metabolic reactions that utilize glucose in glycolysis and the citric acid cycle (see **Figure 1**). A decrease in the activity of thiamin-dependent enzymes limits the conversion of pyruvate to acetyl-CoA and the utilization of the citric acid cycle, leading to accumulation of pyruvate and lactate. Lactic acidosis, a condition resulting from the accumulation of lactate, is often associated with nausea, vomiting, and severe abdominal pain in a syndrome described as gastrointestinal beriberi (8).

Causes of thiamin deficiency

Thiamin deficiency may result from inadequate thiamin intake, increased requirement for thiamin, excessive loss of thiamin from the body, consumption of anti-thiamin factors in food, or a combination of these factors.

Inadequate intake

Inadequate consumption of thiamin is the main cause of thiamin deficiency in developing countries (2). Thiamin deficiency is common in low-income populations whose diets are high in carbohydrate and low in thiamin (e.g., milled or polished rice). Breast-fed infants whose mothers are thiamin deficient are vulnerable to developing infantile beriberi. Alcoholism, which is associated with low intake of thiamin among other nutrients, is the primary cause of thiamin deficiency in industrialized countries. Some of the non-alcoholic conditions associated with WKS include anorexia nervosa, bariatric surgery (weight-loss surgery), gastrointestinal malignancies, and malabsorption syndromes (14-17). Obese individuals may also be at heightened risk of thiamin deficiency (18, 19). Moreover, cases of Wernicke’s encephalopathy have been linked with hyperemesis gravidarum (severe nausea and vomiting during pregnancy) (20, 21), and with parenteral nutrition lacking vitamin supplementation (22, 23).

Increased requirement

Conditions resulting in an increased requirement for thiamin include strenuous physical exertion, fever, pregnancy, breast-feeding, and adolescent growth. Such conditions place individuals with marginal thiamin intake at risk for developing symptomatic thiamin deficiency.

Malaria patients in Southeast Asia were found to be thiamin deficient more frequently than non-infected individuals (24, 25). Malarial infection leads to a large increase in the metabolic demand for glucose. Because thiamin is required for enzymes involved in glucose metabolism, the stresses induced by malarial infection could exacerbate thiamin deficiency in predisposed individuals. HIV-infected individuals, whether or not they had developed AIDS, were also found to be at increased risk for thiamin deficiency (26). Further, chronic alcohol abuse impairs intestinal absorption and utilization of thiamin (1); thus, alcoholics have increased requirements for thiamin. Thiamin deficiency is also observed as a complication of the refeeding syndrome: the introduction of carbohydrates in severely starved individuals leads to an increased demand for thiamin in glycolysis and the citric acid cycle that precipitates thiamin deficiency (27).

Excessive loss

Excessive loss of thiamin may precipitate thiamin deficiency. By increasing urinary flow, diuretics may prevent reabsorption of thiamin by the kidneys and increase its excretion in the urine (28, 29). The risk of thiamin deficiency is increased in diuretic-treated patients with marginal thiamin intake (30) and in individuals receiving long-term, diuretic therapy (31). Individuals with kidney failure requiring hemodialysis lose thiamin at an increased rate and are at risk for thiamin deficiency (32). Alcoholics who maintain a high fluid intake and high urine flow rate may also experience increased loss of thiamin, exacerbating the effects of low thiamin intake (33).

Anti-thiamin factors (ATF)

The presence of anti-thiamin factors (ATF) in foods contributes to the risk of thiamin deficiency. Certain plants contain ATF, which react with thiamin to form an oxidized, inactive product. Consuming very large amounts of tea or coffee (including decaffeinated), as well as chewing tea leaves and betel nuts, might lower thiamin status due to the presence of ATF (34, 35). ATF include mycotoxins (molds) and thiaminases that break down thiamin in food. Individuals who habitually eat certain raw fresh-water fish, raw shellfish, or ferns are at higher risk of thiamin deficiency because these foods contain thiaminase that normally is inactivated by heat in cooking (1, 6). In Nigeria, an acute, neurologic syndrome (seasonal ataxia) has been associated with thiamin deficiency precipitated by a thiaminase in African silkworms, a traditional, high-protein food for some Nigerians (36).

The Recommended Dietary Allowance (RDA)

The RDA for thiamin, revised in 1998 by the Food and Nutrition Board of the Institute of Medicine, was based on the prevention of deficiency in generally healthy individuals (37; **Table 1**).

Table 1. Recommended Dietary Allowance (RDA) for Thiamin

Life Stage	Age	Males (mg/day)	Females (mg/day)
Infants	0-6 months	0.2 (AI)	0.2 (AI)
Infants	7-12 months	0.3 (AI)	0.3 (AI)
Children	1-3 years	0.5	0.5
Children	4-8 years	0.6	0.6
Children	9-13 years	0.9	0.9
Adolescents	14-18 years	1.2	1.0
Adults	19 years and older	1.2	1.1
Pregnancy	all ages	-	1.4
Breast-feeding	all ages	-	1.4

Disease Prevention

Cataracts

A cross-sectional study of 2,900 Australian men and women, 49 years of age and older, found that those in the highest quintile of thiamin intake were 40% less likely to have nuclear cataracts than those in the lowest quintile (38). In addition, a study in 408 US women found that higher dietary intakes of thiamin were inversely associated with five-year change in lens opacification (39). However, these cross-sectional associations have yet to be elucidated by studies of causation.

Diabetes mellitus and vascular complications

Patients with diabetes mellitus have been reported to have low plasma concentrations and high renal clearance of thiamin (40, 41), suggesting that individuals with type 1 or type 2 diabetes are at increased risk for thiamin deficiency. Two thiamin transporters, thiamin transporter-1 (THTR-1) and THTR-2, are involved in thiamin uptake by enterocytes in the small intestine and re-uptake in the proximal tubules of the kidneys. One study suggested that hyperglycemia in patients with diabetes could affect thiamin re-uptake by decreasing the expression of thiamin transporters in the kidneys (42). Conversely, thiamin deficiency appears to impair the normal endocrine function of the pancreas and exacerbate hyperglycemia. Early studies showed that insulin synthesis and secretion were altered in the endocrine pancreatic cells of thiamin-deficient rats (43, 44). In humans, thiamin deficiency caused by recessive mutations in the gene encoding THTR-1 leads to diabetes mellitus in the thiamin-responsive megaloblastic anemia syndrome (see Metabolic diseases below).

In a randomized, double-blind pilot study, high-dose thiamin supplements (300 mg/day) were given for six weeks to hyperglycemic individuals (either glucose intolerant or newly diagnosed with type 2 diabetes). Thiamin supplementation prevented any further increase in fasting glucose and insulin concentrations compared with placebo treatment but did not reduce the hyperglycemia (45). However, one study suggested that thiamin supplementation might improve fasting glucose concentrations in in early stages of type 2 diabetes (i.e., pre-diabetes) (46).

Disease Treatment

Alzheimer's disease

Some older adults are at increased risk for developing subclinical thiamin deficiency secondary to poor dietary intake, reduced gastrointestinal absorption, and multiple medical conditions (47, 48). Since thiamin deficiency can result in a form of dementia (Wernicke-Korsakoff syndrome), its relationship to Alzheimer's disease (AD) and other forms of dementia have been investigated. AD is characterized by a decline in cognitive function in elderly people, accompanied by pathologic features that include β-amyloid plaque deposition and neurofibrillary tangles formed by hyperphosphorylated Tau protein (49).

Using positron emission tomography (PET) scanning, reduced glucose metabolism has been observed in brains of AD patients (50). A large, multicenter PET study using a radiolabeled glucose analog, 18F-Fluoro-deoxyglucose (FDG), correlated a reduction in FDG uptake (a surrogate marker for glucose metabolism) with the extent of cognitive impairment in AD patients. This study, which included 822 subjects over 55 years of age that were cognitively normal (n=229), displayed mild cognitive impairment (n=405), or had mild AD (n=188), demonstrated that brain glucose utilization could predict the progression from mild cognitive impairment to AD (51). A nine-year longitudinal study associated the presence of diabetes mellitus in older people (above 55 years old) with an increased risk for developing AD (52). Emerging evidence links type 2 diabetes and AD, conditions that may involve insulin resistance in the brain (reviewed in 53).

A reduction in thiamin-dependent processes in the brain appears to be related to the altered glucose metabolism in patients with AD (54-56). Case-control studies have found blood levels of thiamin, TPP, and TMP to be lower in those with dementia of Alzheimer's type (DAT) compared to control subjects (57, 58). Moreover, several investigators have found evidence of decreased activity of TPP-dependent enzymes, α-ketoglutarate dehydrogenase and transketolase, in the brains of patients who died of AD (59). The finding of decreased brain levels of TPP in the presence of normal levels of free thiamin and TMP suggests altered TPP synthesis rather than poor thiamin bioavailability. However, it is not clear whether the activities of TPP-metabolizing enzymes (including thiamin pyrophosphokinase) are altered in AD patients (60, 61). Chronic administration of the thiamin derivative benfotiamine alleviated cognitive alterations and decreased the number of β-amyloid plaques in a mouse model of AD without increasing TMP and TPP levels in the brain. This suggested that the beneficial effects of benfotiamine in the brain were likely mediated by the stimulation of TPP-independent pathways (62). Chronic benfotiamine administration was also shown to decrease the number of neurofibrillary tangles in certain brain regions and improve survival in a mouse model (63). In a rat model of neurodegeneration, long-term oral benfotiamine supplementation increased thiamin pyrophosphate concentrations and led to improvements in insulin signaling and cognitive deficits (64).

Thiamin deficiency has been linked to increased β-amyloid production in cultured neuronal cells and to plaque formation in animal models (65, 66). These pathological hallmarks of AD could be reversed by thiamin supplementation, suggesting that thiamin could be protective in AD. Other disorders, including mitochondrial dysfunction and chronic oxidative stress, have been linked to both thiamin deficiency and AD pathogenesis and progression (13, 55, 67). Presently, there is only slight and inconsistent evidence that thiamin supplements are of benefit in AD. A double-blind, placebo-controlled study of 15 patients (10 completed the study) reported no beneficial effect of 3 grams/day of thiamin on cognitive decline over a 12-month period (68). A preliminary report from another study claimed a mild benefit of 3 to 8 grams of thiamin per day in DAT, but no additional data from that study are available (69). A mild beneficial effect in patients with AD was reported after 12 weeks of treatment with 100 mg/day of a thiamin derivative (thiamin tetrahydrofurfuryl disulfide), but this study was not placebo-controlled (70). A 2001 systematic review of randomized, double-blind, placebo-controlled trials of thiamin in patients with DAT found no evidence that thiamin was a useful treatment for the symptoms of Alzheimer's disease (71). More recently, a small uncontrolled study in five patients with mild-to-moderate AD reported cognitive improvement, measured by the Mini-Mental Status Examination, following supplementation with 300 mg/day of benfotiamine for 18 months (72). In a placebo-controlled study of 70 β-amyloid positive patients with either amnestic mild cognitive impairment (a precursor to AD) or mild AD, those receiving 600 mg/day of benfotiamine for 12 months experienced less cognitive decline compared to placebo, but the differences did not reach statistical significance (p=0.125; 73). Large-scale, randomized controlled trials are needed to determine whether supplemental thiamin or benfotiamine might help slow progression of cognitive decline in those with Alzheimer’s disease.

Huntington’s disease

Huntington’s disease is an inherited neurodegenerative disorder characterized by selective degeneration of nerve cells known as striatal spiny neurons. Symptoms, such as movement disorders and impaired cognitive function, typically develop in the fourth decade of life and progressively deteriorate over time. A recent study found decreased levels of the thiamin transporter-2 (THTR-2) protein in the striatum and frontal cortex of patients with Huntington’s disease compared to age-and sex-matched healthy controls (74). Compared to control subjects, this study also found lower concentrations of TPP in the striatum and lower concentrations of TMP in the cerebrospinal fluid of patients with Huntington’s disease (74). Mutations in the *SLC19A3* gene that encodes THTR-2 causes biotin-thiamin-responsive basal ganglia disease, which is treated with high-dose co-supplementation with biotin and thiamin for life (see Biotin-thiamin-responsive basal ganglia disease below). In a mouse model of Huntington’s disease, high-dose supplementation with both of these vitamins improved neuropathological and motor deficits but had no effect on lifespan (p=0.15) (74). A phase II, open-label clinical trial evaluating the effect of combined thiamin-biotin supplementation, at moderate (600 mg/day of thiamin and 150 mg/day of biotin) and high (1,200 mg/day of thiamin and 300 mg/day of biotin) dosages, in Huntington’s disease is currently underway (75).

Congestive heart failure

Severe thiamin deficiency (wet beriberi) can lead to impaired cardiac function and ultimately congestive heart failure (CHF). Although cardiac manifestations of beriberi are rarely encountered in industrialized countries, CHF due to other causes is common, especially in the elderly. Loop diuretics used in the treatment of CHF, notably furosemide, increase thiamin excretion, potentially leading to thiamin deficiency (76, 77). Patients with CHF might also have altered thiamin metabolism, including reduced absorption of thiamin in the small intestine (78). A 2015 meta-analysis of nine observational studies found a 2.5 times higher risk of thiamin deficiency in patients with heart failure compared to control subjects (78). As in the general population, older CHF patients were found to be at higher risk of thiamin deficiency than younger ones (79).

An important measure of cardiac function in CHF is the left ventricular ejection fraction (LVEF), which can be assessed by echocardiography. One study in 25 patients found that furosemide use at doses of 80 mg/day or greater was associated with a 98% prevalence of thiamin deficiency (31). In a randomized, double-blind study of 30 CHF patients, all of whom had been taking furosemide (80 mg/day) for at least three months, intravenous (IV) thiamin therapy (200 mg/day) for seven days resulted in an improved LVEF compared to IV placebo (80). When all 30 of the CHF patients in that study subsequently received six weeks of oral thiamin therapy (200 mg/day), the average LVEF improved by 22%. This finding may be relevant because improvements in LVEF have been associated with improved survival in CHF patients (81). However, clinical trials of oral thiamin supplementation in heart failure patients have not found any benefit. In a randomized, double-blind, placebo-controlled trial in 52 patients with systolic heart failure, 300 mg/day of supplemental thiamin for one month did not improve LVEF compared to placebo (82). A randomized, double-blind, placebo-controlled trial in 64 patients with heart failure reported that 200 mg/day or supplemental thiamin for six months did not improve LVEF (83).

Although little evidence supports the routine use of supplemental thiamin in CHF patients, trials specifically in CHF patients with marginal thiamin status have not been done, and some suggest that it may be prudent to screen patients on long-term diuretic therapy for thiamin deficiency and treat accordingly (84).

Type 2 diabetes mellitus and vascular complications

Chronic hyperglycemia in individuals with diabetes mellitus contributes to the pathogenesis of microvascular diseases. Diabetes-related vascular damage can affect the heart (cardiomyopathy), kidneys (nephropathy), retina (retinopathy), and peripheral nervous system (neuropathy). In subjects with diabetes, hyperglycemia alters the function of bone marrow-derived endothelial progenitor cells (EPC) that are critical for the growth of blood vessels (85). Interestingly, a higher daily intake of thiamin from the diet was correlated with more circulating EPC and with better vascular endothelial health in 88 individuals with type 2 diabetes (86). An inverse association has also been found between plasma concentrations of thiamin and the presence of soluble vascular adhesion molecule-1 (sVCAM-1), a marker of vascular dysfunction, in patients with diabetes (40, 87). Early markers of diabetic nephropathy include the presence of serum albumin in the urine, known as microalbuminuria. Administration of thiamin or benfotiamine (a thiamin derivative) prevented the development of renal complications in chemically-induced diabetic rats (88). A randomized, double-blind, placebo-controlled study conducted in 40 patients with type 2 diabetes with microalbuminuria found that high-dose thiamin supplementation (300 mg/day) decreased excretion of urinary albumin over a three-month period (87). Since thiamin treatment has shown promising results in cultured cells and animal models (89-91), the effects of thiamin and its derivatives on vascular complications should be examined in patients with diabetes.

Cancer

Thiamin deficiency and Wernicke-Korsakoff syndrome have been observed in some cancer patients with rapidly growing tumors (92, 93). Research in cell culture and animal models indicates that rapidly dividing cancer cells have a high requirement for thiamin (94). All rapidly dividing cells require nucleic acids at an increased rate, and some cancer cells appear to rely heavily on the TPP-dependent enzyme, transketolase, to provide the ribose-5-phosphate necessary for nucleic acid synthesis. One study found that the levels of THTR-1, transketolase, and TPP mitochondrial transporters were increased in samples of human breast cancer tissue compared to normal tissue, suggesting an adaptation in thiamin homeostasis in support of cancer metabolism (95). Other studies have found that the gene encoding THTR-2 is downregulated in certain cancers (96). Moreover, use of the chemotherapeutic drug, 5-fluorouracil, inhibits phosphorylation of thiamin to thiamin pyrophosphate and may thus lead to thiamin deficiency (97, 98).

Thiamin supplementation in cancer patients is common to prevent thiamin deficiency, but Boros et al. caution that too much thiamin may actually fuel the growth of some malignant tumors (99), suggesting that thiamin supplementation be reserved for those cancer patients who are actually deficient in thiamin. Presently, there is no evidence available from studies in humans to support or refute this theory. However, it would be prudent for individuals with cancer who are considering thiamin supplementation to discuss it with the clinician managing their cancer therapy. Intravenous, high-dose thiamin has been suggested as a treatment for cancer patients with confirmed Wernicke-Korsakoff (93).

Sepsis

Sepsis is a life-threatening critical illness caused by a dysregulated host response to an infection. The widespread inflammation can lead to tissue and organ damage and to death (100). Because thiamin deficiency is common among septic patients (101), several studies have investigated the treatment effect of intravenous thiamin – alone or in combination with other agents like vitamin C and hydrocortisone.

Observational studies examining the association of intravenous thiamin as a monotherapy have mainly looked at its association with lactic acidosis, which commonly occurs in both thiamin deficiency and sepsis, and with mortality. One retrospective study in 123 septic patients and 246 matched controls found that intravenous thiamin administration within 24 hours of hospital admission was linked to improvements in both lactate clearance and 28-day mortality (102). In a small retrospective study of 53 alcohol-use disorder patients presenting with septic shock, lower mortality was observed in the 34 patients who received intravenous thiamin compared to the 19 patients who did not (103).

A few randomized controlled trials have evaluated the effect of intravenous thiamin in the treatment of sepsis. A randomized, double-blind, placebo-controlled trial in 88 patients with sepsis and elevated blood concentrations of lactate reported that intravenous thiamin (200 mg twice daily for seven days or until discharge from the hospital) did not decrease lactate concentrations at 24 hours post initiation of treatment – the primary endpoint of the trial (104). No differences between the treatment and placebo groups were found for the secondary endpoints, which included survival (104). In a subsequent analysis of data from this trial, the septic patients that were given parenteral thiamin (n=31) had lower creatinine concentrations throughout the treatment and were less likely to need renal replacement therapy compared to placebo (n=39; 105).

A 2020 meta-analysis of four studies – one observational and three randomized controlled trials – found no benefit of intravenous thiamin for improving lactate concentrations, length of hospital stay in intensive care, or overall survival (106). Large-scale clinical trials are needed to determine whether parenteral administration of thiamin is beneficial in the treatment of sepsis. Administering thiamin in combination with vitamin C and corticosteroids may be more efficacious to treat sepsis (107); some clinical trials of such treatments are currently underway (see clinicaltrials.gov/).

Metabolic diseases

Thiamin supplementation is included in the clinical management of genetic diseases that affect the metabolism of carbohydrates and branched-chain amino acids (BCAAs).

Thiamin-responsive pyruvate dehydrogenase complex (PDHC) deficiency

Mutations in PDHC prevent the efficient oxidation of carbohydrates in affected individuals. PDHC deficiency is commonly characterized by lactic acidosis, neurologic and neuromuscular degeneration, and death during childhood. The patients who respond to thiamin treatment (from a few mg/day to doses above 1,000 mg/day) exhibit PDHC deficiency due to the decreased affinity of PDHC for TPP (108, 109). Although thiamin supplementation can reduce lactate accumulation and improve the clinical features in thiamin-responsive patients, it does not constitute a cure (110).

Maple syrup urine disease

Inborn errors of BCAA metabolism lead to thiamin-responsive branched-chain ketoaciduria, also known as maple syrup urine disease. Alterations in the BCAA catabolic pathway result in neurologic dysfunction caused by the accumulation of BCAAs and their derivatives, branched-chain ketoacids (BCKA). The therapeutic approach includes a synthetic diet with reduced BCAA content, and thiamin (10-1,000 mg/day) is supplemented to patients with mutations in the E2 subunit of the BCKDH complex (111). In thiamin-responsive individuals, the supplementation has been proven effective to correct the phenotype without recourse to the BCAA restriction diet.

Thiamin-responsive megaloblastic anemia

Mutations in the *SLC19A2* gene that encodes THTR-1 impairs intestinal thiamin uptake and causes thiamin deficiency, leading to thiamin-responsive megaloblastic anemia (112). This syndrome, which is also called thiamin metabolism dysfunction syndrome-1, is characterized by megaloblastic anemia, diabetes mellitus, and deafness. A review of 30 cases reported additional neurologic, visual, and cardiac impairments (113). High-dose oral supplementation with thiamin (up to 300 mg/day) helps to maintain health and correct hyperglycemia in prepubescent children. A recent study in 32 individuals with found no additional benefit of oral doses above 150 mg/day (114). After puberty, a decline in pancreatic function results in the requirement of insulin together with thiamin to control the hyperglycemia. One study also reported that the treatment of a four-month-old girl with 100 mg/day of thiamin did not prevent hearing loss at 20 months of age (115). Early diagnosis of the syndrome and early treatment with thiamin is important for a better prognosis (114).

Biotin-thiamin-responsive basal ganglia disease

Biotin-thiamin-responsive basal ganglia disease (also called biotin-responsive basal ganglia disease, thiamin transporter-2 deficiency, and thiamin metabolism dysfunction syndrome-2) is caused by an autosomal recessive mutation in the *SLC19A3* gene that codes for THTR-2. The disease usually presents around 3 to 10 years of age (116), but an early infantile form of the disease exists with onset as early as one month of age (117). Clinical features include subacute encephalopathy (confusion, drowsiness, altered level of consciousness), ataxia, and seizures.

A retrospective study of 18 affected individuals from the same family or the same tribe in Saudi Arabia showed that biotin monotherapy (5-10 mg/kg/day) efficiently abolished the clinical manifestations of the disease, although one-third of the patients suffered from recurrent acute crises. Often associated with poor outcomes, acute crises were not observed for a five-year follow-up period following thiamin supplementation (300-400 mg/day) – early diagnosis and immediate treatment with biotin and thiamin led to positive outcomes (118). Recent studies have found supplemental thiamin to be important in treating the condition. In an open-label study of 20 pediatric patients with the disease, supplemental thiamin alone was as effective as combined biotin-thiamin supplementation when given for 30 months (119). Lifelong high-dose supplementation with a combination of biotin and thiamin is generally the treatment for biotin-thiamin-responsive basal ganglia disease (116). Early diagnosis and treatment is important to ensure a better prognosis (117, 120).

Other thiamin metabolism dysfunction syndromes

Supplemental thiamin has limited utility in treating other inborn errors of thiamin metabolism. Mutations in the *SLC25A19* gene that codes for the mitochondrial TPP transporter can result in either thiamin metabolism dysfunction syndrome-3 (THMD3) or thiamin metabolism dysfunction syndrome-4 (THMD4). Of these rare syndromes, THMD3 (also called Amish-type microcephaly or Amish lethal microcephaly) has the more severe phenotype, resulting in a congenital microcephaly, elevated concentrations of α-ketoglutarate in urine, and usually death in infancy (121). THMD4 is characterized by episodic encephalopathy and weakness, which often presents following a viral infection or febrile illness in childhood. Some patients affected with THMD4 may respond to high-dose thiamin supplementation (122).

Mutations in the *TPK1* gene result in thiamin pyrophosphokinase 1 deficiency and thiamin metabolism dysfunction syndrome-5 (THMD5), which usually manifests in early childhood. While the clinical presentation of THMD5 varies, affected individuals often experience episodic ataxia, dystonia, and lactic acidosis (123). Only a few cases of THMD5 have been reported to date; two of these patients experienced limited improvement of symptoms upon supplementation with thiamin, in conjunction with adherence to a high-fat diet (124).

Sources

Humans obtain thiamin from dietary sources and from the normal microflora of the colon, although the contribution of the latter towards the body’s requirement for thiamin is not clear (125).

Food sources

A varied diet should provide most individuals with adequate thiamin to prevent deficiency. In the US the average dietary thiamin intake for young adult men is about 2 mg/day and 1.2 mg/day for young adult women. A survey of people over the age of 60 found an average dietary thiamin intake of 1.4 mg/day for men and 1.1 mg/day for women (37). However, institutionalization and poverty both increase the likelihood of inadequate thiamin intake in the elderly (126). Whole-grain cereals, legumes (e.g., beans and lentils), nuts, lean pork, and yeast are rich sources of thiamin (1). Because most of the thiamin is lost during the production of white flour and polished (milled) rice, white rice and foods made from white flour (e.g., bread and pasta) are fortified with thiamin in many Western countries. A number of thiamin-rich foods are listed in the table below, along with their thiamin content in milligrams (mg). For more information on the nutrient content of foods, search USDA's FoodData Central.

Table 2. Some Food Sources of Thiamin

Food	Serving	Thiamin (mg)
Lentils (cooked, boiled)	½ cup	0.17
Green peas (cooked, boiled)	½ cup	0.21
Long-grain, brown rice (cooked)	½ cup	0.18
Long-grain, white rice, enriched (cooked)	½ cup	0.13
Long-grain, white rice, unenriched (cooked)	½ cup	0.016
Whole-wheat bread	1 slice	0.13
White bread, enriched	1 slice	0.31
Fortified breakfast cereal (wheat, puffed)	1 cup	0.31
Wheat germ breakfast cereal (toasted, plain)	1 cup	1.88
Pork, lean (loin, tenderloin, cooked, roasted)	3 ounces*	0.80
Pecans	1 ounce (19 halves)	0.19
Spinach (cooked, boiled)	½ cup	0.09
Orange	1 fruit	0.11
Cantaloupe	½ fruit	0.11
Milk	1 cup	0.10
Egg (cooked, hard-boiled)	1 large	0.03
*Three ounces of meat is a serving about the size of a deck of cards		

Supplements

Thiamin is available in dietary supplements and in fortified foods, most commonly as thiamin hydrochloride or thiamin mononitrate (127). Multivitamin supplements typically contain at least 1.2 mg of thiamin, the Daily Value (DV) for adults and children 4 years and older (128).

Benfotiamine is a synthetic, lipid-soluble precursor of thiamin that is available as a dietary supplement. It has higher bioavailability compared to thiamin (129).

Safety

Toxicity

The Food and Nutrition Board did not set a tolerable upper intake level (UL) for thiamin because there are no well-established toxic effects from consumption of excess thiamin in food or through long-term, oral supplementation (up to 200 mg/day). A small number of life-threatening anaphylactic reactions have been observed with large intravenous doses of thiamin (37).

Drug interactions

Reduced blood concentrations of thiamin have been reported in individuals with seizure disorders (epilepsy) taking the anticonvulsant medication, phenytoin, for long periods of time (130). 5-Fluorouracil, a drug used in cancer therapy, inhibits the phosphorylation of thiamin to TPP (131). Diuretics, especially furosemide, may increase the risk of thiamin deficiency in individuals with marginal thiamin intake due to increased urinary excretion of thiamin (29). Moreover, chronic alcohol abuse is associated with thiamin deficiency due to low dietary intake, impaired absorption and utilization, and increased excretion of the vitamin (1). Chronic alcohol feeding to rats showed a decrease in the active absorption of thiamin linked to the inhibition of thiamin membrane transporter THTR-1 in the intestinal epithelium (132). Alcohol consumption in rats also decreases the levels of THTR-1 and THTR-2 in renal epithelial cells, thus limiting thiamin re-uptake by the kidneys (133).

Linus Pauling Institute Recommendation

The Linus Pauling Institute supports the recommendation by the Food and Nutrition Board of 1.2 mg/day of thiamin for men and 1.1 mg/day for women. A varied diet should provide enough thiamin for most people. Following the Linus Pauling Institute recommendation to take a daily multivitamin/mineral supplement, containing 100% of the Daily Values (DV), will ensure an intake of at least 1.5 mg/day of thiamin.

Older adults (>50 years)

Presently, there is no evidence that the requirement for thiamin is increased in older adults, but some studies have found inadequate dietary intake and thiamin insufficiency to be more common in elderly populations (126). Thus, it would be prudent for older adults to take a multivitamin/mineral supplement, which will generally provide at least 1.5 mg/day of thiamin.

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Vitamin A

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Summary

- Vitamin A is a generic term that refers to fat-soluble compounds found as preformed vitamin A (retinol) in animal products and as provitamin A carotenoids in fruit and vegetables. The three active forms of vitamin A in the body are retinol, retinal, and retinoic acid. *(More information)*
- Vitamin A is involved in regulating the growth and specialization (differentiation) of virtually all cells in the human body. Vitamin A has important roles in embryonic development, organ formation during fetal development, normal immune functions, and eye development and vision. *(More information)*
- Vitamin A deficiency is a major cause of preventable blindness in the world. It is most prevalent among children and women of childbearing age. Vitamin A deficiency is associated with an increased susceptibility to infections, as well as to thyroid and skin disorders. *(More information)*
- The recommended dietary allowance (RDA) is 700 micrograms of retinol activity equivalents (μg RAE)/day for women and 900 μg RAE/day for men. *(More information)*
- Vitamin A prophylaxis appears to significantly reduce childhood mortality in regions at high risk of vitamin A deficiency. Further, high-dose vitamin A supplementation is widely recommended for children over six months of age when they are infected with measles while malnourished, immunodeficient, or are at risk of measles complications. *(More information)*
- Retinoic acid and analogs are used at pharmacological doses in the treatment of acute promyelocytic leukemia and various skin diseases. *(More information)*
- Animal food sources rich in preformed vitamin A include dairy products, liver, and fish oils; fortified cereals may also contain preformed vitamin A. Rich sources of provitamin A carotenoids include orange and green vegetables, such as sweet potato and spinach. *(More information)*
- Overconsumption of preformed vitamin A can be highly toxic and is especially contraindicated prior to and during

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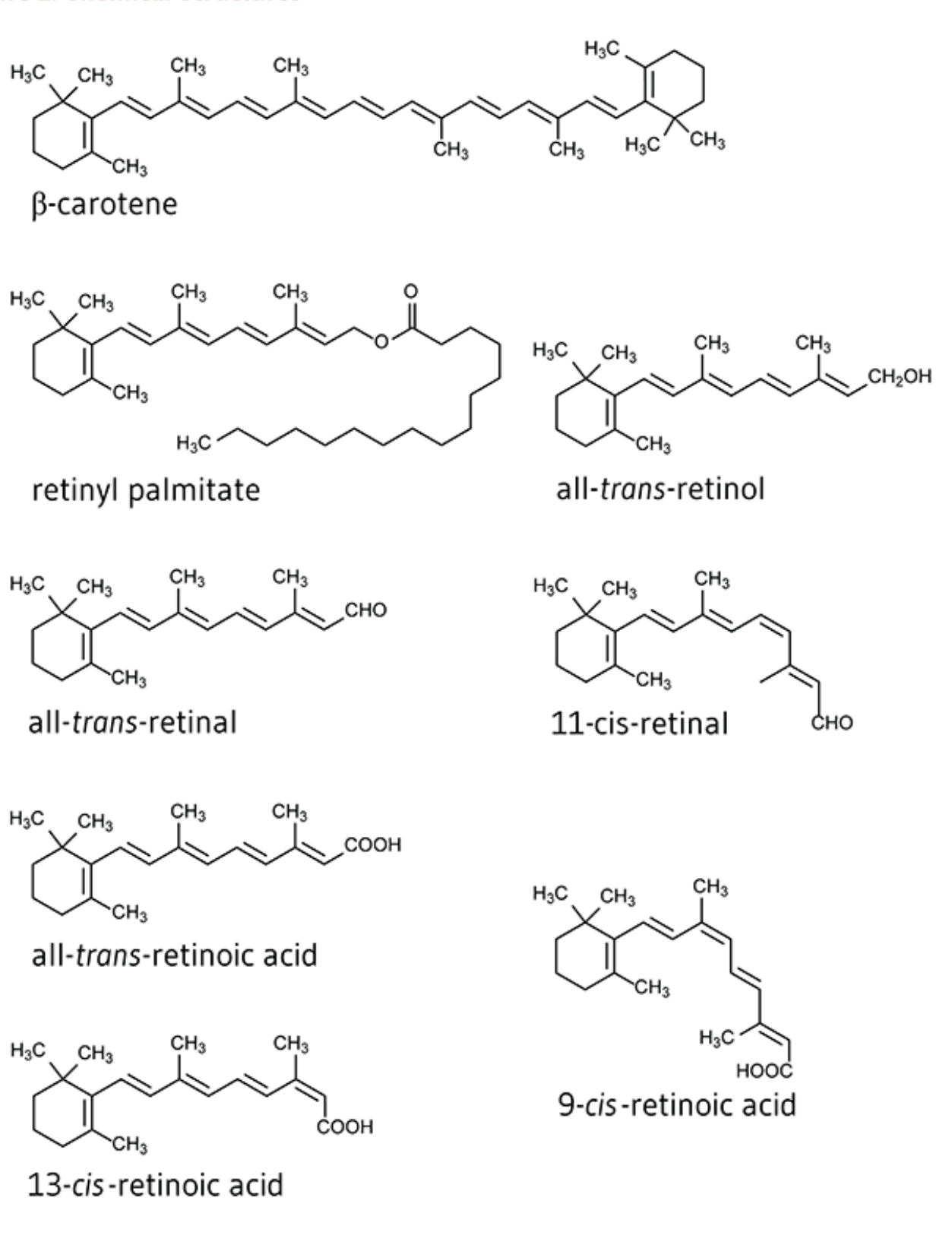
pregnancy as it can result in severe birth defects. The tolerable upper intake level (UL) for vitamin A in adults is set at 3,000 μg RAE/day. The UL does not apply to vitamin A derived from carotenoids. (More information)

Vitamin A is a generic term that encompasses a number of related compounds (**Figure 1**). Retinol and retinyl esters are often referred to as preformed vitamin A. Retinol can be converted by the body to retinal, which can be in turn be oxidized to retinoic acid, the form of vitamin A known to regulate gene transcription. Retinol, retinal, retinoic acid, and related compounds are known as retinoids. β-Carotene and other food carotenoids that can be converted by the body into retinol are referred to as provitamin A carotenoids (see the article on Carotenoids). Hundreds of different carotenoids are synthesized by plants, but only about 10% of them are capable of being converted to retinol (1). The following discussion will focus mainly on preformed vitamin A compounds and retinoic acid.

Figure 1. Chemical Structures



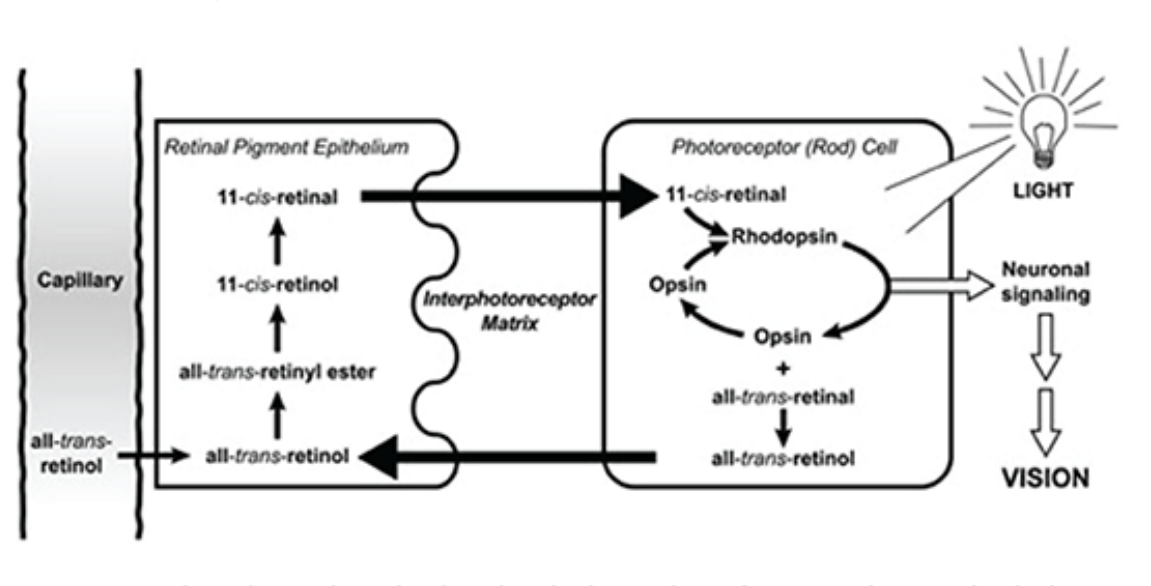
Function

Vitamin A compounds are essential fat-soluble molecules predominantly stored in the liver in the form of retinyl esters (e.g., retinyl palmitate). When appropriate, retinyl esters are hydrolyzed to generate all-*trans*-retinol, which binds to retinol binding protein (RBP) before being released in the bloodstream. The all-*trans*-retinol/RBP complex circulates bound to the protein, transthyretin, which delivers all-*trans*-retinol to peripheral tissues (reviewed in 2). Vitamin A as retinyl esters in chylomicrons was also found to have an appreciable role in delivering vitamin A to extrahepatic tissues, especially in early life (3, 4).

Visual system and eyesight

Located at the back of the eye, the retina contains two main types of light-sensitive receptor cells – known as rod and cone photoreceptor cells. Photons (particles of light) that pass through the lens are sensed by the photoreceptor cells of the retina and converted to nerve impulses (electric signals) for interpretation by the brain. All-*trans*-retinol is transported to the retina via the circulation and accumulates in retinal pigment epithelial (RPE) cells (**Figure 2**) (5). Here, all-*trans*-retinol is esterified to form a retinyl ester, which can be stored. When needed, retinyl esters are broken apart (hydrolyzed) and isomerized to form 11-*cis*-retinol, which can be oxidized to form 11-*cis*-retinal. 11-*cis*-retinal can be shuttled across the interphotoreceptor space to the rod photoreceptor cell that is specialized for vision in low-light conditions and for detection of motion. In rod cells, 11-*cis*-retinal binds to a protein called opsin to form the visual pigment rhodopsin (also known as visual purple). Absorption of a photon of light catalyzes the isomerization of 11-*cis*-retinal to all-*trans*-retinal that is released from the opsin molecule. This photoisomerization triggers a cascade of events, leading to the generation of a nerve impulse conveyed by the optic nerve to the brain's visual cortex. All-*trans*-retinal is converted to all-*trans*-retinol and transported across the interstitial space to the RPE cells, thereby completing the visual cycle.

Figure 2. The Visual Cycle



Retinol is transported to the retina via the circulation, where it moves into retinal pigment epithelial cells. There, retinol is esterified to form a retinyl ester that can be stored. When needed, retinyl esters are broken apart (hydrolyzed) and isomerized to form 11-*cis*-retinol, which can be oxidized to form 11-*cis*-retinal. 11-*cis*-retinal can be shuttled to the rod cell, where it binds to a protein called opsin to form the visual pigment, rhodopsin (also known as visual purple). Absorption of a photon of light catalyzes the isomerization of 11-*cis*-retinal to all-*trans*-retinal and results in its release. This isomerization triggers a cascade of events, leading to the generation of an electrical signal to the optic nerve. The nerve impulse generated by the optic nerve is conveyed to the brain where it can be interpreted as vision. Once released, all-*trans*-retinal is converted to all-*trans*-retinol, which can be transported across the interphotoreceptor matrix to the retinal epithelial cell to complete the visual cycle.

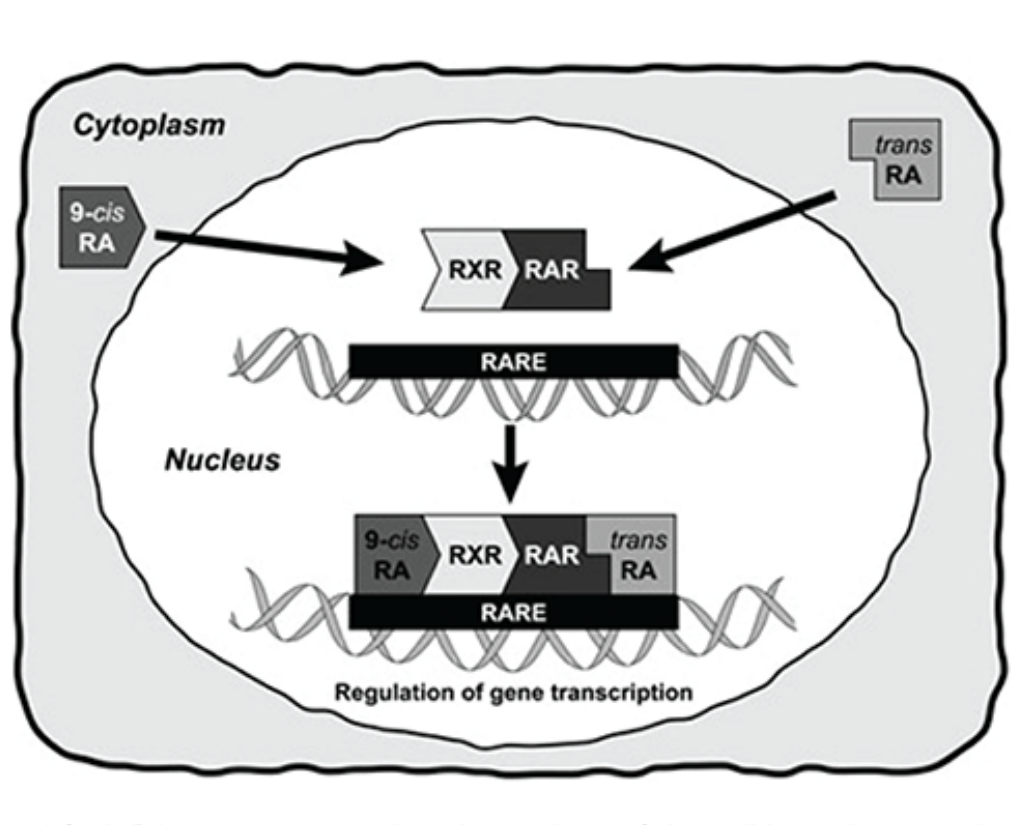
A similar cycle occurs in cone cells that contain red, green, or blue opsin proteins required for the absorption of photons from the visible light spectrum (2). Vitamin A is also essential for mammalian eye development (6). Thus, because vitamin A is required for the normal functioning of the retina, dim-light vision, and color vision, inadequate retinol and retinal available to the retina result in impaired dark adaptation. In the severest cases of vitamin A deficiency, thinning and ulceration of the cornea leads to blindness (see Deficiency).

Regulation of gene expression

Regulatory capacity of retinoic acid

In cells, all-*trans*-retinol can be either stored (in the form of retinyl ester) or oxidized to all-*trans*-retinal by alcohol dehydrogenases. In turn, retinaldehyde dehydrogenases can catalyze the conversion of all-*trans*-retinal into two biologically active isomers of retinoic acid (RA): all-*trans*-RA and 9-*cis*-RA. RA isomers act as hormones to affect gene expression and thereby influence numerous physiological processes. All-*trans*-RA and 9-*cis*-RA are transported to the nucleus of the cell bound to cellular retinoic acid-binding proteins (CRABP). Within the nucleus, RA isomers bind to specific nuclear receptor proteins that are ligand-dependent transcription factors (**Figure 3**). Both all-*trans*-RA and 9-*cis*-RA can bind to retinoic acid receptors (RARα, RARβ, and RARγ), whereas only 9-*cis*-RA binds to retinoid X receptors (RXRα, RXRβ, and RXRβ) (7). RAR and RXR subtypes form either complexes of two of the same protein (RAR/RAR and RXR/RXR homodimers) or complexes of two different proteins (RAR/RXR heterodimers). RAR/RXR heterodimers can bind to a regulatory DNA sequence called retinoic acid response element (RARE) located within the promoter of retinoid-responsive genes. The transcriptional activity of RAR/RXR heterodimers appears to be mainly driven by the binding of all-*trans*-RA to RAR.

Figure 3. A Simplified Model of the Regulation of Gene Expression by Retinoic Acid (RA) Isomers



All-*trans*-RA and 9-*cis*-RA are transported to the nucleus of the cell bound to cytoplasmic retinoic acid-binding proteins. Within the nucleus, all-*trans*-RA binds to retinoic acid receptors (RAR) and 9-*cis*-RA binds to retinoid receptors (RXR). RAR and RXR form RAR/RXR heterodimers, which bind to regulatory regions of the chromosome called retinoic acid response elements (RARE). Binding of all-*trans*-RA and 9-*cis*-RA to RAR and RXR respectively allows the complex to regulate the rate of gene transcription.

The activation of RAR by RA binding triggers the recruitment of transcriptional coregulators to target promoters, thereby inhibiting or allowing the transcription of genes (8). RXR also forms heterodimers with several other nuclear receptors, including thyroid hormone receptor (TR), vitamin D receptor (VDR), steroid receptors, and peroxisome proliferator-activated receptor (PPAR) (9). In this way, vitamin A may interact with thyroid hormone, vitamin D, steroids (e.g., estrogen), or PPAR ligands signaling pathways and influence the transcription of a broad range of genes.

There is also evidence that RA/RAR can affect gene expression in a RARE-independent manner. For example, it was reported that RAR could interfere with TGFβ/Smad signaling pathway through direct interaction of RAR with the heterodimeric transcription factor, Smad3/Smad4. In the absence of RA, RAR was found to act as a coactivator of Smad3/Smad4-mediated transcription, while RAR agonists repressed the transcriptional activity of Smad3/Smad4 (10). In retinoblastoma cells, RAR was also involved in RA-induced activation of signaling cascades mediated by tyrosine kinases known as phosphoinositide 3-kinase (PI3K) and leading to cell differentiation (11, 12). RA also appeared to induce neuronal differentiation by activating ERK1/2 MAP kinase signaling pathway that phosphorylated transcription factor, CREB (cyclic AMP response element binding protein). Phosphorylated CREB can subsequently bind to the CREB response element in the promoter of genes involved in cell differentiation (13). Also, independently of RAR, RA was found to inhibit ERK1/2 phosphorylation/activation and subsequent AP1-mediated expression of interleukin-6 in synovial cells (14). Hence, RA can influence the expression of genes whose promoters do not contain RARE.

By regulating the expression of over 500 retinoid-responsive genes (including several genes involved in vitamin A metabolism itself), retinoic acid isomers play major roles in cellular proliferation and differentiation (i.e., cell commitment to highly specialized functions).

Regulatory capacity of retinol

In the eye and tissues like white adipose and muscle, retinol plasma membrane receptor/transporter STRA6 accepts retinol from extracellular RBP and unloads it to intracellular retinol-binding protein (CRBP). STRA6 also cooperates with lecithin:retinol acyltransferase (LRAT), an enzyme that catalyzes retinol esterification and storage, to maintain an inward concentration gradient of retinol (15). Interestingly, retinol uptake by STRA6 was found to trigger the activation of a signaling cascade mediated by tyrosine kinases known as Janus kinases (JAK) and associated transcription factors (STAT). JAK/STAT signaling pathway regulates the expression of a wide range of cytokines, hormones, and growth factors (16). Animal studies have reported that an increased expression of genes, such as *SOCS3* by the JAK/STAT pathway, could result in the inhibition of insulin signaling. Hence, obese mice lacking LRAT or STRA6 appear to be protected from retinol/STRA6-induced insulin resistance (17, 18).

Regulatory capacity of retinal

Apart from its role as a ligand for opsin in the visual cascade (see Visual system and eyesight), retinal has been specifically implicated in the regulation of genes important for lipid metabolism. In humans, two types of adipose tissue have been distinguished based on their respective functions: white adipose tissue (WAT) stores fatty acids as triglycerides, and brown adipose tissue (BAT) oxidizes fatty acids to generate heat (thermogenesis). In the mitochondrial respiratory chain of brown adipose cells, the processes of electron transport and ATP production are uncoupled (dissociated) to permit the rapid production of heat from fatty acid oxidation (19).

Retinaldehyde dehydrogenase 1 (RALDH1), which converts retinal to retinoic acid, is highly expressed in WAT but not in BAT. The suppression of RALDH1 expression in WAT can induce a thermogenic phenotype resembling that of BAT (20). During adipocyte differentiation, the stimulation of cells with all-*trans* retinal has been found to activate the *UCP1* gene required for thermogenesis while inhibiting genes promoting adipogenesis, such as *PPARγ* (20). Retinal also appeared to regulate lipid metabolism and adiposity in bone marrow by inhibiting PPARγ/RXR heterodimer-mediated gene expression (21). In addition, retinal was found to inhibit gluconeogenic gene expression and glucose production in the liver of mice deficient in RALDH1 (22).

Immunity

Vitamin A was initially coined "the anti-infective vitamin" because of its importance in the normal functioning of the immune system (23). The skin and mucosal cells, lining the airways, digestive tract, and urinary tract function as a barrier and form the body's first line of defense against infection. Retinoic acid (RA) is produced by antigen-presenting cells (APCs), including macrophages and dendritic cells, found in these mucosal interfaces and associated lymph nodes. RA appears to act on dendritic cells themselves to regulate their differentiation, migration, and antigen-presenting capacity. In addition, the production of RA by APCs is required for the differentiation of naïve CD4 T-lymphocytes into induced regulatory T-lymphocytes (Tregs). Critical to the maintenance of mucosal integrity, the differentiation of Tregs is driven by all-*trans*-RA through RARα-mediated regulation of gene expression (see Regulation of gene expression). Also, during inflammation, all-*trans*-RA/RARα signaling pathway promotes the conversion of naïve CD4 T-lymphocytes into effector T-lymphocytes – type 1 helper T-cells (Th1) – (rather than into Tregs) and induces the production of proinflammatory cytokines by effector T-lymphocytes in response to infection. There is also substantial evidence to suggest that RA may help prevent the development of autoimmunity (reviewed in 24).

Prenatal and postnatal development

Both vitamin A excess and deficiency are known to cause birth defects. Retinoid signaling begins soon after the early phase of embryonic development known as gastrulation. During fetal development, RA is critical for the development of organs, including the heart, eyes, ears, lungs, as well as other limbs and visceral organs. Vitamin A has been implicated in fetal lung maturation (2). Vitamin A status is lower in preterm newborns than in full-term infants (25). There is some evidence to suggest that vitamin A supplementation may help reduce the incidence of chronic lung disease and mortality in preterm newborns (see Disease Prevention). Retinoid signaling is also involved in the expression of many proteins of the extracellular matrix (ECM; material surrounding cells), including collagen, laminin, and proteoglycans (26). Vitamin A deficiency may then result in alterations of the ECM composition, thus disrupting organ morphology and function (reviewed in 26).

Red blood cell production (erythropoiesis)

Red blood cells (erythrocytes), like all blood cells, are derived from pluripotent stem cells in the bone marrow. Studies involving *in vitro* culture systems have suggested a role for retinoids in stem cell commitment and differentiation to the red blood cell lineage. Retinoids might also regulate apoptosis (programmed cell death) of red blood cell precursors (erythropoietic progenitor cells) (27). However, whether retinoids regulate erythropoiesis *in vivo* has not been established. Yet, vitamin A supplementation in vitamin A deficient-individuals has been shown to increase hemoglobin concentrations. Additionally, vitamin A appears to facilitate the mobilization of iron from storage sites to the developing red blood cell for incorporation into hemoglobin, the oxygen carrier in red blood cells (27, 28).

Nutrient interactions

Zinc

Zinc deficiency is thought to interfere with vitamin A metabolism in several ways (29): (1) zinc deficiency results in decreased synthesis of retinol-binding protein (RBP), which transports retinol through the circulation to peripheral tissues and protects the organism against potential toxicity of retinol; (2) zinc deficiency results in decreased activity of the enzyme that releases retinol from its storage form, retinyl palmitate, in the liver; and (3) zinc is required for the enzyme that converts retinol into retinal (30). The health consequences of zinc deficiency on vitamin A nutritional status in humans are yet to be defined (29).

Iron

Vitamin A deficiency often coexists with iron deficiency and may exacerbate iron deficiency anemia by altering iron metabolism (27). Vitamin A supplementation has beneficial effects on iron deficiency anemia and improves iron nutritional status among children and pregnant women (27, 28). The combination of supplemental vitamin A and iron seems to reduce anemia more effectively than either supplemental iron or vitamin A alone (31). Moreover, studies in rats have shown that iron deficiency alters plasma and liver levels of vitamin A (32, 33).

Deficiency

Vitamin A deficiency usually results from inadequate intakes of vitamin A from animal products (as preformed vitamin A) and fruit and vegetables (as provitamin A carotenoids). In developing countries, vitamin A deficiency and associated disorders predominantly affect children and women of reproductive age. Other individuals at risk of vitamin A deficiency are those with poor absorption of lipids due to impaired pancreatic or biliary secretion and those with inflammatory bowel diseases, such as Crohn's disease and celiac disease (2). Subclinical vitamin A deficiency is often defined by serum retinol concentrations lower than 0.70 μmol/L (20 μg/dL). In severe vitamin A deficiency, vitamin A body stores are depleted and serum retinol concentrations fall below 0.35 μmol/L (10 μg/dL). Other biomarkers have been calibrated to assess vitamin A nutritional status (reviewed in 34). Of note, the World Health Organization considers vitamin A deficiency a public health problem when the prevalence of low serum retinol (<0.70 μmol/L) reaches 15% or more of a defined population.

Vitamin A deficiency-related disorders

Disease of the eye and blindness

With an estimated 250,000 to 500,000 children becoming blind annually, vitamin A deficiency constitutes the leading preventable cause of blindness in low- and middle-income nations (35). The earliest symptom of vitamin A deficiency is impaired dark adaptation known as night blindness or nyctalopia. The next clinical stage is the occurrence of abnormal changes in the conjunctiva (corner of the eye), manifested by the presence of Bitot's spots. Severe or prolonged vitamin A deficiency eventually results in a condition called xerophthalmia (Greek for dry eye), characterized by changes in the cells of the cornea (clear covering of the eye) that ultimately result in corneal ulcers, scarring, and blindness (36). Immediate administration of 200,000 international units (IU) of vitamin A for two consecutive days is required to prevent blinding xerophthalmia (36).

There is an estimated 19.1 million pregnant women worldwide (especially in Sub-Saharan Africa, Southeast Asia, and Central America) with vitamin A deficiency and over half of them are affected by night blindness (37). The prevalence of vitamin A deficiency and night blindness is especially high during the third trimester of pregnancy due to accelerated fetal growth. Also, approximately 190 million preschool-age children have low serum retinol concentrations (<0.70 μmol/L), with 5.2 million suffering from night blindness. Moreover, half of the children affected by severe vitamin A deficiency-induced blinding xerophthalmia are estimated to die within a year of becoming blind (37). The World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) promote vitamin A supplementation as a public health intervention to reduce child mortality in areas and populations where vitamin A deficiency is prevalent (38-40).

Susceptibility to infectious diseases

Infectious diseases have been associated with depletion of vitamin A hepatic reserves (already limited in vitamin A-deficient subjects), reduced serum retinol concentrations, and increased loss of vitamin A in the urine (37). Infection with the measles virus was found to precipitate conjunctival and corneal damage, leading to blindness in children with poor vitamin A status (41). Conversely, vitamin A deficiency can be considered a nutritionally acquired immunodeficiency disease (42). Even children who are only mildly deficient in vitamin A have a higher incidence of respiratory complications and diarrhea, as well as a higher rate of mortality from measles infection compared to children consuming sufficient vitamin A (43). Because vitamin A supplementation may decrease both the severity and incidence of measles complications in developing countries (see Disease Prevention), WHO recommends that children aged at least one year receive 200,000 IU of vitamin A (60 mg RAE) for two consecutive days in addition to standard treatment when they are infected with measles virus and live in areas of vitamin A deficiency (44).

A recent prospective cohort study, conducted in 2,774 Colombian children (ages, 5-12 years old) followed for a median 128 days, also reported an inverse relationship between plasma retinol concentrations and rates of diarrhea with vomiting and cough with fever, the latter being a strong predictor of influenza infection (flu) (45). A review of five randomized, placebo-controlled studies that included 7,528 HIV-positive pregnant or breast-feeding women found no substantial benefit of vitamin A supplementation in reducing the mother-to-child transmission of HIV (46). One early observational study found that HIV-infected women who were vitamin A deficient were three to four times more likely to transmit HIV to their infants (47). Yet, no trial to date has provided any information on potential adverse effects of vitamin A supplementation on mother-to-child HIV transmission (48).

Thyroid dysfunction

In North and West Africa, vitamin A deficiency and iodine deficiency induced-goiter can coexist in up to 50% of children. The response to iodine prophylaxis in iodine-deficient populations appears to depend on various nutritional factors, including vitamin A status (49, 50). Vitamin A deficiency in animal models was found to interfere with the pituitary-thyroid axis by (1) increasing the synthesis and secretion of thyroid-stimulating hormone (TSH) by the pituitary gland, (2) increasing the size of the thyroid gland, (3) reducing iodine uptake by the thyroid gland and impairing the synthesis and iodination of thyroglobulin, and (4) increasing circulating concentrations of thyroid hormones (reviewed in 51). A cross-sectional study of 138 children with concurrent vitamin A and iodine deficiencies found that the severity of vitamin A deficiency was associated with higher risk of goiter and higher concentrations of circulating TSH and thyroid hormones (50). These children received iodine-enriched salt with either vitamin A (200,000 IU at baseline and 5 months) or placebo in a randomized, double-blind, 10-month trial. This vitamin A supplementation significantly decreased TSH concentration and thyroid volume compared to placebo (50). In another trial, supplementation of vitamin A to iodine-deficient children had no additional effect to iodine on thyroid status compared to placebo, but vitamin A supplementation alone (without iodine) reduced the volume of the thyroid gland, as well as TSH and thyroglobulin concentrations (52).

Other disorders

Phrynoderma or follicular hyperkeratosis is a skin condition characterized by an excessive production of keratin in hair follicles. The lesions first appear on the extremities, shoulders, and buttocks and may spread over the entire body in the severest cases (53). While vitamin A deficiency may contribute to the occurrence of phrynoderma, the condition has been strongly associated with multiple nutritional deficiencies and is considered a sign of general malnutrition. A rare case of esophagitis (inflammation of the esophagus) has recently been attributed to hyperkeratosis secondary to vitamin A deficiency (54).

Also, vitamin A deficiency affects iron mobilization, impairs hemoglobin synthesis, and precipitates iron deficiency anemia that is only alleviated with supplementation of both vitamin A and iron (see Nutrient interactions) (27).

The Recommended Dietary Allowance (RDA)

Retinol Activity Equivalents (RAE)

Vitamin A can be obtained from food as preformed vitamin A in animal products or as provitamin A carotenoids in fruit and vegetables (see Food sources). Yet, while preformed vitamin A is effectively absorbed, stored, and hydrolyzed to form retinol, provitamin A carotenoids like β-carotene are less easily digested and absorbed, and must be converted to retinol and other retinoids by the body after uptake into the small intestine. The efficiency of conversion of provitamin A carotenes into retinol is highly variable, depending on factors such as food matrix, food preparation, and one's digestive and absorptive capacities (55).

The most recent international standard of measure for vitamin A is retinol activity equivalents (RAE), which represent vitamin A activity as retinol. It has been determined that 2 micrograms (μg) of β-carotene in oil provided as a supplement could be converted by the body to 1 μg of retinol giving it an RAE ratio of 2:1. However, 12 μg of β-carotene from food are required to provide the body with 1 μg of retinol, giving dietary β-carotene an RAE ratio of 12:1. Other provitamin A carotenoids in food are less easily absorbed than β-carotene, resulting in RAE ratios of 24:1. RAE ratios are shown in **Table 1** (56).

Table 1. Retinol activity equivalents (RAE) Ratios for Preformed Vitamin A and Provitamin A Carotenoids

Quantity Consumed	Quantity Bioconverted to Retinol	RAE Ratio
1 μg of dietary or supplemental vitamin A	1 μg of retinol*	1:1
2 μg of supplemental β-carotene	1 μg of retinol	2:1
12 μg of dietary β-carotene	1 μg of retinol	12:1
24 μg of dietary α-carotene	1 μg of retinol	24:1
24 μg of dietary β-cryptoxanthin	1 μg of retinol	24:1

*1 IU is equivalent to 0.3 microgram (μg) of retinol, and 1 μg of retinol is equivalent to 3.33 IU of retinol.

Determination of the RDA

The RDA for vitamin A was revised by the Food and Nutrition Board (FNB) of the US Institute of Medicine (IOM) in 2001. The RDA is based on the Estimated Average Requirement (EAR), which is defined as the biological requirement for 50% of the population. The RDA is the recommended intake needed by nearly all of the population to ensure adequate hepatic stores of vitamin A in the body (20 μg/g for four months if the person consumes a vitamin A-deficient diet) to support normal reproductive function, immune function, gene expression, and vision (for details of calculations, see 56). **Table 2** lists the RDA values in micrograms (μg) of Retinol Activity Equivalents (RAE) per day.

Table 2. Recommended Dietary Allowance (RDA) for Vitamin A as Preformed Vitamin A (micrograms [μg] of Retinol Activity Equivalents [RAE]/day)

Life Stage	Age	Males (μg/day)	Females (μg/day)
Infants	0-6 months	400 (AI)	400 (AI)
Infants	7-12 months	500 (AI)	500 (AI)
Children	1-3 years	300	300
Children	4-8 years	400	400
Children	9-13 years	600	600
Adolescents	14-18 years	900	700
Adults	19 years and older	900	700
Pregnancy	18 years and younger	-	750
Pregnancy	19 years and older	-	770
Breast-feeding	18 years and younger	-	1,200
Breast-feeding	19 years and older	-	1,300

Disease Prevention

Bronchopulmonary dysplasia in preterm infants

Preterm infants are born with inadequate body stores of vitamin A, placing them at risk of developing diseases of the eye and the respiratory and gastrointestinal tracts. About one-third of preterm infants born between 22 and 28 weeks of gestation develop bronchopulmonary dysplasia (BPD), a chronic lung disease that can be fatal or result in life-long morbidities in survivors. A few randomized controlled studies have investigated the effect of postnatal vitamin A supplementation on the incidence of BPD and the risk of mortality in very low birth weight infants (≤1,500 g) requiring respiratory support (57-59). In the largest, multicenter, randomized, blinded, placebo-controlled trial that enrolled 807 extremely low birth weight (ELBW; ≤1,000 g) preterm newborns, the intramuscular administration of 5,000 IU of vitamin A three times a week for four weeks significantly, though modestly, reduced the risk of BPD or death at 36 weeks' postmenstrual age (gestational age plus chronological age) (58). While vitamin A supplementation was included in some neonatal programs after this trial (60), a national shortage in vitamin A supply that has affected US neonatal intensive care units since 2010 has led to a significant reduction in the use of vitamin A supplementation in premature newborns (401-1,000 g at birth) with respiratory failure (61, 62). However, a retrospective analysis of US nationwide data from 6,210 preterm infants born between 2010 and 2012 found that a reduction in vitamin A prophylaxis from 27.2% to 2.1% during the same period had no significant impact on the incidence of BPD or death before hospital discharge (62).

In another retrospective study, the nonrandomized use of vitamin A supplementation with inhaled nitric oxide (iNO) was found to result in a lower incidence of BPD (but not mortality) compared to iNO therapy alone in preterm newborns with a birth weight of 750-999 g (63). Neurodevelopment index scores at one year of age were also improved in the vitamin A group of newborns weighing 500-749 g at birth. Yet, caution is advised with the interpretation of the results, especially because the trial was not designed to assess the effect of vitamin A. In Germany, one large, multicenter, randomized study – the NeoVitaA trial – is under way to explore the effect of high-dose oral vitamin A (5,000 IU/kg/day) for 28 days on the incidence of BPD and mortality at 36 weeks' postmenstrual age (64).

While high doses of vitamin A during early pregnancy can cause birth defects (see Safety), vitamin A supplementation during late pregnancy may improve maternal and fetal vitamin A status (65). Although a few randomized controlled trials have failed to show an effect on maternal and neonatal mortality (66), more research is required to assess whether vitamin A supplementation during pregnancy reduces BPD incidence in infants.

Childhood morbidity and mortality

A recent meta-analysis of randomized controlled trials evaluating the preventive effect of vitamin A on childhood mortality indicated that vitamin A supplementation (200,000 IU every 4 or 6 months) reduced all-cause mortality by 25% (13 studies) and diarrhea-specific mortality by 30% (7 studies) in children aged 6 to 59 months. However, vitamin A administration in this age group had no preventive effect on rates of pneumonia-specific mortality (7 studies), measles-specific mortality (5 studies), or meningitis-specific mortality (3 studies). Moreover, no reduction in the risk of disease-specific mortality was found in neonates (0 to 28 days of age) and infants 1 to 6 months of age supplemented with vitamin A (67). Another meta-analysis of randomized controlled trials found no evidence of a reduction in mortality risk during infancy when either breast-feeding mothers (7 studies) or infants aged less than six months (9 studies) were supplemented with vitamin A (68).

Current WHO policy recommends vitamin A supplementation at routine vaccination contacts in children after six months of age living in regions at high risk of vitamin A deficiency. Supplementation with high doses of vitamin A – 100,000 IU (30 mg RAE) for infants 6 to 11 months of age and 200,000 IU (60 mg RAE) for children 12 to 59 months of age – is thought to provide adequate protection for up to six months (38). A recent placebo-controlled trial in Guinea-Bissau, which randomized 7,587 children (ages, 6 to 23 months old) to receive vitamin A supplementation at one vaccination contact, evaluated the co-administration of vitamin A and vaccines on child mortality (69). The study found that vitamin A supplementation had no effect on overall mortality rates, although a six-month follow-up of infants given both measles and DTP (diphtheria-tetanus-pertussis) vaccinations showed a significant reduction in mortality in girls, but not in boys (69). Although neonatal vitamin A supplementation is not currently recommended, a trial assessing the benefit of early measles vaccination – at 4.5 rather than the usual 9 months of age – found no reduction in mortality rates when children had received neonatal vitamin A supplementation (70). The recent pooled analysis of previous trials of vitamin A supplementation (VITA I-III) in Guinea-Bissau confirmed that vitamin A supplementation may interfere with vaccines. Specifically, compared to placebo, neonatal vitamin A supplementation was associated with a significant increase in mortality rates in boys (but not in girls) when children had received measles virus vaccination at 4.5 months of age rather than the usual 9 months of age (71). The timing of vitamin A interventions needs to be further examined in relation to the timing of vaccinations in order to maximize their benefits.

Complications from measles infection

An earlier meta-analysis of seven randomized controlled trials examining specifically the role of vitamin A supplementation in 2,069 children with measles found no overall reduction on the risk of mortality (72). Yet, the pooled analysis of four studies that reported the age distribution of participants found an 83% lower risk of mortality with two doses of 200,000 IU of vitamin A in children younger than two years. In addition, the pooled analysis of three studies indicated a 67% reduction in the risk of pneumonia-led mortality (72). Similar to WHO and UNICEF guidelines, the American Academy of Pediatrics recommends vitamin A supplementation for children over six months of age when they are infected with measles while malnourished, immunodeficient, or are at risk of measles complications or vitamin A deficiency disorders (73). Although measles infection has been associated with vitamin A deficiency and blindness, there is currently no evidence to suggest that vitamin A supplementation reduces the risk of blindness in children infected with measles (74).

Cancer

Studies in cell culture and animal models have documented the capacity for natural and synthetic retinoids to reduce carcinogenesis significantly in skin, breast, liver, colon, prostate, and other sites. However, the results of human studies examining the relationship between the consumption of preformed vitamin A and cancer do not currently suggest that consuming vitamin A at intakes greater than the RDA benefit in the prevention of cancer (2).

Lung cancer

The results of the β-Carotene And Retinol Efficacy Trial (CARET) have suggested that high-dose supplementation of preformed vitamin A and β-carotene should be avoided in people at high risk for lung cancer (75). In the CARET study, about 9,000 people (smokers and people with asbestos exposure) were assigned a daily regimen of 25,000 IU (7,500 μg RAE) of retinyl palmitate and 30 mg of β-carotene, while a similar number of people were assigned a placebo. After four years of follow-up, the incidence of lung cancer was 28% higher in the supplemented group compared to the placebo group; however, the incidence was not different six years after the intervention ended (76). A possible explanation for an increase in lung cancer is that the oxidative environment of the lung, created by smoke or asbestos exposure, could give rise to unusual carotenoid cleavage products, which might promote carcinogenesis (77). Interestingly, a case-control study that included 749 lung cancer cases and 679 controls from the CARET trial found a significant association between lung cancer risk reduction and high vitamin D intakes (≥400 IU/day) in individuals who received the active CARET supplements or in those with vitamin A intakes equal to or greater than 1,500 μg RAE/day (78). Further, a recent meta-analysis of four randomized controlled trials, including a total of 202,924 participants at low risk of lung cancer, indicated that supplementation with retinol and/or β-carotene had no significant effect on lung cancer incidence (79). At present, it seems unlikely that increased intake of preformed vitamin A (e.g., retinol) could lower the risk of lung cancer.

Disease Treatment

Retinoids may be used at pharmacological doses to treat several conditions, including, acute promyelocytic leukemia, retinitis pigmentosa, and various skin diseases. It is important to note that treatment with high doses of natural or synthetic retinoids overrides the body's own control mechanisms; therefore, retinoid therapies are associated with potential side effects and toxicities. Additionally, all of the retinoid compounds have been found to cause fetal deformations. Thus, women who have a chance of becoming pregnant should avoid treatment with these medications. Retinoids tend to be very long acting: side effects and birth defects have been reported to occur months after discontinuing retinoid therapy (2). The retinoids discussed below are prescription drugs and should not be used without medical supervision.

Acute promyelocytic leukemia

Normal differentiation of myeloid stem cells in the bone marrow gives rise to platelets, red blood cells, and white blood cells (also called leukocytes) that are important for the immune response. Altered differentiation of myeloid cells can result in the proliferation of immature white blood cells, giving rise to leukemia. Reciprocal chromosome translocations involving the promyelocytic leukemia (PML) gene and the gene coding for retinoic acid receptor α (RARα) lead to a specific type of leukemia called acute promyelocytic leukemia (APL). The fusion protein PML/RARα represses transcription by binding to RARE in the promoter of retinoid-responsive genes involved in hematopoietic cell differentiation. Gene repression by PML/RARα is achieved by the recruitment of several chromatin modifiers, including histone deacetylases (HDACs) and DNA methyltransferases (DNMTs). Contrary to RARα wild-type receptor, PML/RARα appears to be insensitive to physiological concentrations of retinoic acid (RA) such that only treatments with high doses of all-*trans*-RA can restore normal differentiation and lead to significant improvements and complete remission in some APL patients (80).

More information on APL treatment programs can be found in the National Cancer Institute website.

Diseases of the skin

Both natural and synthetic retinoids have been used as pharmacologic agents to treat disorders of the skin. Acitretin is a synthetic retinoid that has been proven useful in combination treatments for psoriasis (81). Topical tretinoin (all-*trans*-retinoic acid) and oral isotretinoin (13-*cis*-retinoic acid) have been used successfully to treat mild-to-severe acne vulgaris (82, 83). Retinoids exhibit anti-inflammatory properties and regulate the proliferation and differentiation of skin epithelial cells, as well as the production of sebum. Use of pharmacological doses of retinoids (especially oral isotretinoin) by pregnant women causes birth defects and is therefore contraindicated prior to and during pregnancy (see Safety in pregnancy).

For more information on the use of retinoids in the management of acne, see the article on Vitamin A and Skin Health.

Retinitis pigmentosa

Retinitis pigmentosa (RP) affects approximately 1.5 million people worldwide and is a leading cause of inherited blindness. RP describes a broad spectrum of genetic disorders that result in the progressive loss of photoreceptor cells (rods and cones) in the retina of the eye (84). While at least 45 loci have been associated with RP, mutations in the rhodopsin gene (*RHO*), the usherin gene (*USH2A*), and the RP GTPase regulator gene (*RPGR*) account for about 30% of all RP cases (85).

Early symptoms of RP include impaired dark adaptation and night blindness, followed by the progressive loss of peripheral and central vision over time (85). The results of only one randomized controlled trial in 601 patients with common forms of RP indicated that supplementation with 15,000 IU/day of retinyl palmitate (4,500 μg RAE) significantly slowed the loss of retinal function over a period of four to six years (86). In contrast, supplementation with 400 IU/day of vitamin E (*dl*-α-tocopherol) modestly but significantly increased the loss of retinal function, suggesting that patients with common forms of RP may benefit from long-term vitamin A supplementation but should avoid high-dose vitamin E supplementation. Up to 12 years of follow-up in these patients did not reveal any signs of liver toxicity as a result of excess vitamin A intake (87). Because neither children younger than 18 years nor adults affected by less common forms of RP were included in the trial, no formal recommendation about vitamins A and E could be made (85). High-dose vitamin A supplementation to slow the course of RP requires medical supervision and must be discontinued if there is a possibility of pregnancy (see Safety).

Sources

Food sources

Free retinol is not generally found in food. Retinyl esters (including retinyl palmitate) are the storage form of retinol in animals and thus the main precursors of retinol in food from animals. Plants contain carotenoids, some of which are precursors for vitamin A (e.g., α-carotene, β-carotene, and β-cryptoxanthin). Yellow- and orange-colored vegetables contain significant quantities of carotenoids. Green vegetables also contain carotenoids, though yellow-to-red pigments are masked by the green pigment of chlorophyll (1). The table below lists a number of good food sources of vitamin A, including fruit and vegetables, along with their vitamin A content. The retinol activity is indicated in micrograms of retinol activity equivalents (μg RAE). For information on this unit of measurement, see the section on RAE. In addition, use USDA's FoodData Central to check foods for their content of carotenoids without vitamin A activity, such as lycopene, lutein, and zeaxanthin.

Vitamin A international units (IUs)

Vitamin A may still be listed on food and supplement labels in international units versus as μg RAE ('mcg' on labels). USDA's FoodData Central also provides the vitamin A content of food sources using the vitamin A international unit (IU). Yet, contrary to RAE, the number of IUs of vitamin A does not reflect the bioavailability of vitamin A from different food sources. Conversion rates between IUs and μg RAE are set as follows:

- 1 IU of retinol is equivalent to 0.3 μg RAE
- 1 IU of supplemental β-carotene is equivalent to 0.3 μg RAE
- 1 IU of dietary β-carotene is equivalent to 0.05 μg RAE
- 1 IU of α-carotene or β-cryptoxanthin to 0.025 μg RAE

Thus, in **Table 3**, the number of IUs of vitamin A in carotenoid-containing food (numbers in italics) can be obtained by multiplying the RAE by approximately 20.

Table 3. Some Food Sources of Vitamin A

Food	Serving	Preformed Vitamin A (Retinol), μg	Vitamin A, μg RAE	Vitamin A, IU
Beef liver, cooked	1 slice (68 g)	6,421*	6,421*	21,566*
Cod liver oil	1 teaspoon	1,350	1,350	4,500
Fortified breakfast cereal (oats)	1 serving (1 oz)	216	216	721
Egg	1 large	80	80	270
Butter	1 tablespoon	95	95	355
Whole milk	1 cup (8 fl oz)	110	110	395
2% fat milk (vitamin A added)	1 cup (8 fl oz)	134	134	464
Nonfat milk (vitamin A added)	1 cup (8 fl oz)	149	149	500
Sweet potato (canned, mashed)	½ cup	0	555	*11,091*
Sweet potato (baked)	½ cup	0	961	*19,218*
Pumpkin (canned)	½ cup	0	953	*19,065*
Carrot (raw, chopped)	½ cup	0	534	*10,692*
Cantaloupe	½ medium melon	0	466	*9,334*
Mango	1 fruit	0	181	*3,636*
Spinach (cooked)	½ cup	0	472	*9,433*
Broccoli (cooked)	½ cup	0	60	*1,207*
Kale (cooked)	½ cup	0	443	*8,854*
Collards (cooked)	½ cup	0	361	*7,220*
Squash, butternut (cooked)	½ cup	0	572	*11,434*

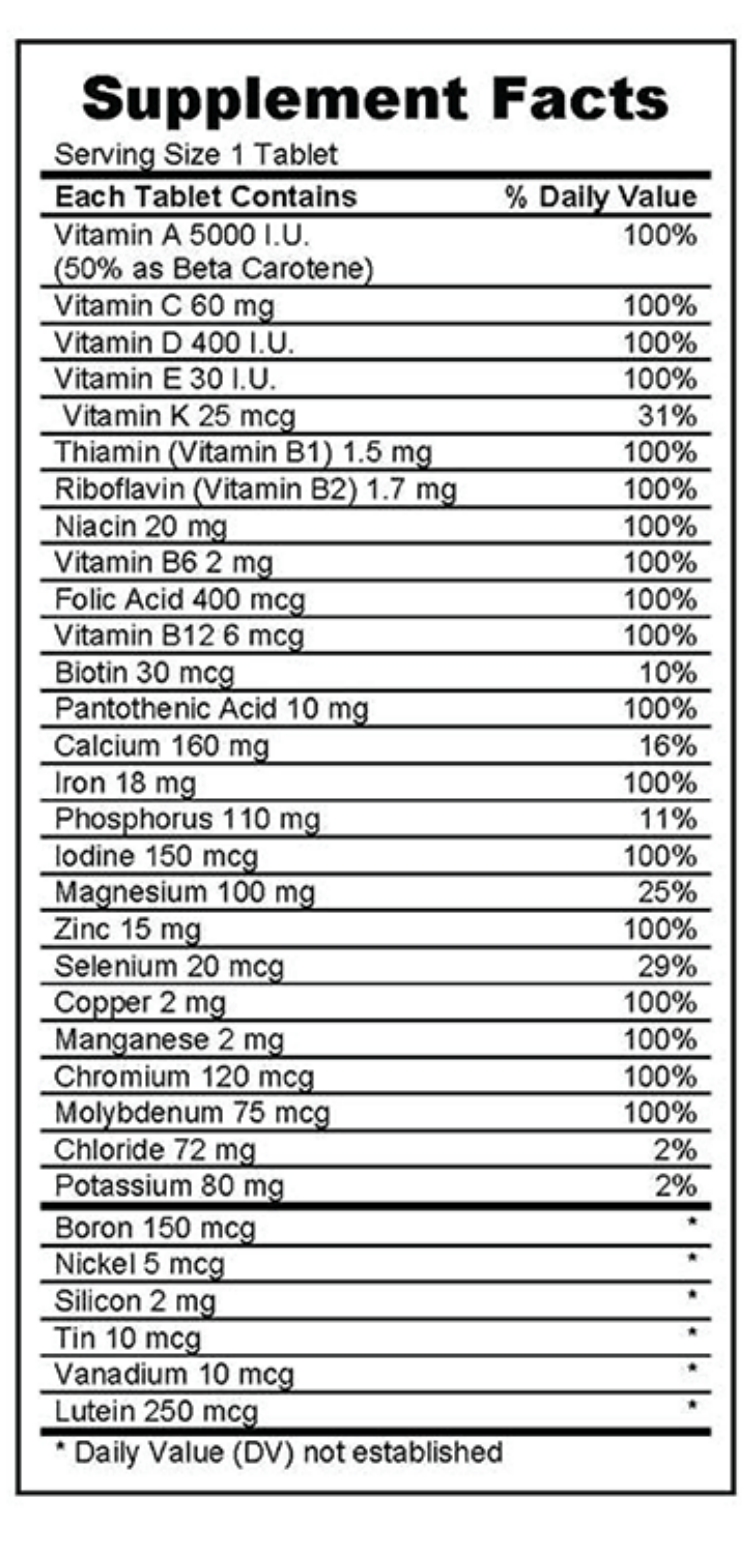
*Above the tolerable upper intake level (UL) of 3,000 μg RAE (10,000 IU)/day

Supplements

The principal forms of preformed vitamin A in supplements are retinyl palmitate and retinyl acetate. β-Carotene is also a common source of vitamin A in supplements, and many supplements provide a combination of retinol and β-carotene (88). If a percentage of the total vitamin A content of a supplement comes from β-carotene, this information is included in the Supplement Facts label under vitamin A (**Figure 4**). Some multivitamin supplements available in the US provide up to 5,000 IU of preformed vitamin A, corresponding to 1,500 μg RAE, which is substantially more than the current RDA for vitamin A. This is due to the fact that the Daily Values (DV) used by the US Food and Drug Administration (FDA) for supplement labeling are based on the RDA established in 1968 rather than the most recent RDA, and multivitamin supplements typically provide 100% of the DV for most nutrients. Because retinol intakes of 5,000 IU/day (1,500 μg RAE) may be associated with an increased risk of osteoporosis in older adults (see Safety), some companies have reduced the retinol content in their multivitamin supplements to 2,500 IU (750 μg RAE).

Figure 4. An Example of a Multivitamin/Mineral Supplement Label

Note: 50% (2,500 IU) of vitamin A is supplied as β-carotene, while the rest (2,500 IU) is supplied as retinol.



Supplement Facts

Serving Size 1 Tablet

Each Tablet Contains	% Daily Value
Vitamin A 5000 I.U. (50% as Beta Carotene)	100%
Vitamin C 60 mg	100%
Vitamin D 400 I.U.	100%
Vitamin E 30 I.U.	100%
Vitamin K 25 mcg	31%
Thiamin (Vitamin B1) 1.5 mg	100%
Riboflavin (Vitamin B2) 1.7 mg	100%
Niacin 20 mg	100%
Vitamin B6 2 mg	100%
Folic Acid 400 mcg	100%
Vitamin B12 6 mcg	100%
Biotin 30 mcg	10%
Pantothenic Acid 10 mg	100%
Calcium 160 mg	16%
Iron 18 mg	100%
Phosphorus 110 mg	11%
Iodine 150 mcg	100%
Magnesium 100 mg	25%
Zinc 15 mg	100%
Selenium 20 mcg	29%
Copper 2 mg	100%
Manganese 2 mg	100%
Chromium 120 mcg	100%
Molybdenum 75 mcg	100%
Chloride 72 mg	2%
Potassium 80 mg	2%
Boron 150 mcg	*
Nickel 5 mcg	*
Silicon 2 mg	*
Tin 10 mcg	*
Vanadium 10 mcg	*
Lutein 250 mcg	*

* Daily Value (DV) not established

Safety

Toxicity

The condition caused by vitamin A toxicity is called hypervitaminosis A. It is caused by overconsumption of preformed vitamin A, not carotenoids. Preformed vitamin A is rapidly absorbed and slowly cleared from the body. Therefore, toxicity from preformed vitamin A may result acutely from high-dose exposure over a short period of time or chronically from a much lower intake (2). Acute vitamin A toxicity is relatively rare, and symptoms include nausea, headache, fatigue, loss of appetite, dizziness, dry skin, desquamation, and cerebral edema. Signs of chronic toxicity include dry itchy skin, desquamation, anorexia, weight loss, headache, cerebral edema, enlarged liver, enlarged spleen, anemia, and bone and joint pain. Also, symptoms of vitamin A toxicity in infants include bulging fontanels. Severe cases of hypervitaminosis A may result in liver damage, hemorrhage, and coma. Generally, signs of toxicity are associated with long-term consumption of vitamin A in excess of 10 times the RDA (8,000-10,000 μg RAE/day or 25,000-33,000 IU/day). However, more research is necessary to determine if subclinical vitamin A toxicity is a concern in certain populations (89). There is evidence that some populations may be more susceptible to toxicity at lower doses, including the elderly, chronic alcohol users, and some people with a genetic predisposition to high cholesterol (90). In January 2001, the Food and Nutrition Board of the US Institute of Medicine set the tolerable upper intake level (UL) of vitamin A intake for adults at 3,000 μg RAE (10,000 IU)/day of preformed vitamin A (56).

Table 4. Tolerable Upper Intake Level (UL) for Preformed Vitamin A

Age Group	μg RAE/day	IU/day*
Infants 0-12 months	600	2,000
Children 1-3 years	600	2,000
Children 4-8 years	900	3,000
Children 9-13 years	1,700	5,667
Adolescents 14-18 years	2,800	9,333
Adults 19 years and older	3,000	10,000

*1 IU of preformed vitamin A is equivalent to 0.3 μg RAE, and 1 μg RAE is equivalent to 3.33 IU of preformed vitamin A

Safety in pregnancy

Although normal fetal development requires sufficient vitamin A intake, consumption of excess preformed vitamin A (such as retinol) during early pregnancy is known to cause birth defects. No increase in the risk of vitamin A-associated birth defects has been observed at doses of preformed vitamin A from supplements below 3,000 μg RAE/day (10,000 IU/day) (56). Of note, in 2011, the World Health Organization (WHO) recommended vitamin A supplementation (up to 3,000 μg RAE/day or 7,500 μg RAE/week) during pregnancy in areas with high prevalence of vitamin A deficiency for the prevention of blindness (91). In industrialized countries, pregnant or potentially pregnant women should monitor their intake of vitamin A from fortified food and food naturally high in preformed vitamin A (e.g., liver) and avoid taking daily multivitamin supplements that contain more than 1,500 μg RAE (5,000 IU) of vitamin A. There is no evidence that consumption of vitamin A from β-carotene might increase the risk of birth defects. The synthetic derivative of retinol, isotretinoin, is known to cause serious birth defects and should not be taken during pregnancy or if there is a possibility of becoming pregnant (82). Tretinoin (all-*trans*-retinoic acid), another retinol derivative, is prescribed as a topical preparation that is applied to the skin. Although percutaneous absorption of topical tretinoin is minimal, its use during pregnancy is not recommended (92).

Do high intakes of vitamin A increase the risk of osteoporosis?

Results from some prospective studies have suggested that long-term intakes of preformed vitamin A in excess of 1,500 μg RAE/day (equivalent to 5,000 IU/day of vitamin A as retinol) were associated with reduced bone mineral density (BMD) and increased risk of osteoporotic fracture in older adults (93-95). However, other investigators failed to observe such detrimental effects on BMD and/or fracture risk (96-98). The recent meta-analysis of four prospective studies, including nearly 183,000 participants over 40 years of age, found that highest vs. lowest quintiles of retinol (preformed vitamin A) intake significantly increased the risk of hip fracture (99). Only excess intakes of retinol, not β-carotene, were associated with adverse effects on bone health. Besides, the pooled analysis of four observational studies also indicated that a U-shaped relationship between circulating retinol and risk of hip fracture, suggesting that both elevated and reduced retinol concentrations in the blood were associated with an increased risk of hip fracture (99).

To date, limited experimental data have suggested that vitamin A (as all-*trans*-retinoic acid) may affect the development of bone-remodeling cells and stimulate bone matrix degradation (resorption) (reviewed in 100). Vitamin A may also interfere with the ability of vitamin D to maintain calcium balance (101). In the large Women's Health Initiative (WHI) prospective study, the highest vs. lowest quintile of retinol intake (≥1,426 μg/day vs. <474 μg/day) was found to be significantly associated with increased risk of fracture only in women with the lowest vitamin D intakes (≤440 IU/day) (102).

Until supplements and fortified food are reformulated to reflect the current RDA for vitamin A, it is advisable for older individuals to consume multivitamin supplements that contain no more than 2,500 IU (750 μg) of preformed vitamin A (usually labeled vitamin A acetate or vitamin A palmitate) and no more than 2,500 IU of additional vitamin A as β-carotene.

Drug interactions

Chronic alcohol consumption results in depletion of liver stores of vitamin A and may contribute to alcohol-induced liver damage (cirrhosis) (103). However, the liver toxicity of preformed vitamin A (retinol) is enhanced by chronic alcohol consumption, thus narrowing the therapeutic window for vitamin A supplementation in alcoholics (103). Oral contraceptives that contain estrogen and progestin increase retinol binding protein (RBP) synthesis by the liver, increasing the export of all-*trans*-retinol/RBP complex to the circulation. Whether this increases the dietary requirement of vitamin A is not known. Also, the use of cholesterol-lowering medications (like cholestyramine and colestipol), as well as orlistat, mineral oil, and the fat substitute, olestra, which interfere with fat absorption, may affect the absorption of fat-soluble vitamins, including vitamin A (88). Further, intake of large doses of vitamin A may decrease the absorption of vitamin K. Retinoids or retinoid analogs, including acitretin, all-*trans*-retinoic acid, bexarotene, etretinate, and isotretinoin, should not be used in combination with single-nutrient vitamin A supplements, because they may increase the risk of vitamin A toxicity (88).

Linus Pauling Institute Recommendation

The RDA for vitamin A (700 μg RAE/day for women and 900 μg RAE/day for men) is sufficient to support normal gene expression, immune function, and vision. However, following the Linus Pauling Institute's recommendation to take a multivitamin/mineral supplement daily could supply as much as 5,000 IU (1,500 μg RAE)/day of vitamin A as retinol, the amount that has been associated with adverse effects on bone health in older adults. For this reason, we recommend taking a multivitamin/mineral supplement that provides no more than 2,500 IU (750 μg) of preformed vitamin A (usually labeled vitamin A acetate or vitamin A palmitate) and no more than 2,500 IU of additional vitamin A as β-carotene. High potency vitamin A supplements should not be used without medical supervision due to the risk of toxicity.

Older adults (>50 years)

Presently, there is little evidence that the requirement for vitamin A in older adults differs from that of younger adults. Additionally, vitamin A toxicity may occur at lower doses in older adults than in younger adults. Further, data from observational studies suggested an association between intakes of preformed vitamin A in excess of 1,500 μg RAE (5,000 IU)/day and increased risk of hip fracture in older people (see Safety). Yet, following the Linus Pauling Institute's recommendation to take a multivitamin/mineral supplement daily could supply as much as 5,000 IU/day of retinol, the amount that has been associated with adverse effects on bone health in older adults. For this reason, we recommend taking a multivitamin/mineral supplement that provides (750 μg) of preformed vitamin A (usually labeled vitamin A acetate or vitamin A palmitate) and no more than 2,500 IU of additional vitamin A as β-carotene. As for all age groups, high potency vitamin A supplements should not be used without medical supervision due to the risk of toxicity.

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Vitamin B6

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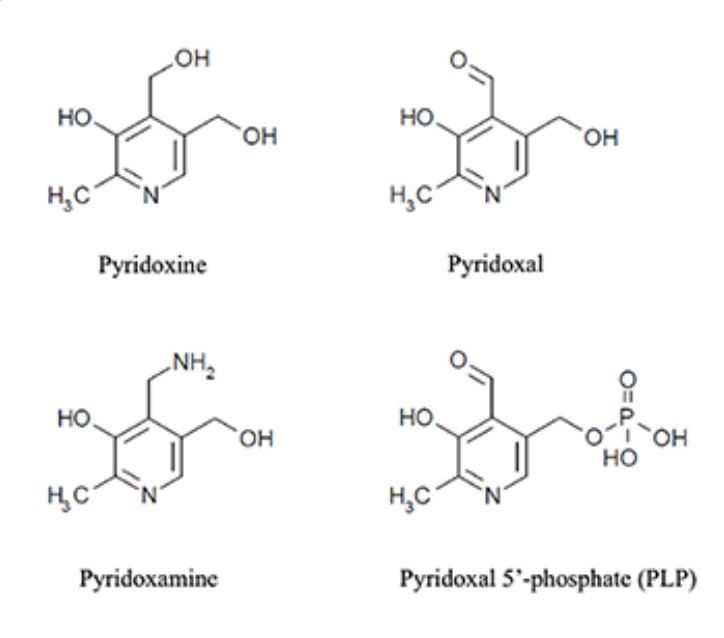
Summary

- Vitamin B_6 and its derivative pyridoxal 5'-phosphate (PLP) are essential to over 100 enzymes mostly involved in protein metabolism. *(More information)*
- High levels of circulating homocysteine are associated with an increased risk of cardiovascular disease. Randomized controlled trials have demonstrated that supplementation with B vitamins, including vitamin B_6, could effectively reduce homocysteine levels. However, homocysteine lowering by B vitamins has failed to lower the risk of adverse cardiovascular outcomes in high-risk individuals. *(More information)*
- Growing evidence from experimental and clinical studies suggests that systemic inflammation underlying most chronic diseases may impair vitamin B_6 metabolism. *(More information)*
- Although supplementation with vitamin B_6 and other B vitamins has not been associated with improved cognitive performance or delayed cognitive deterioration in the elderly, recent studies suggest that vitamin B_6 might help reduce the risk of late-life depression. *(More information)*
- Pharmacologic doses of vitamin B_6 are used to treat seizures in rare inborn errors of vitamin B_6 metabolism. Also, randomized controlled trials support the use of vitamin B_6 to treat morning sickness in pregnant women and suggest a possible benefit in the management of premenstrual syndrome and carpal tunnel syndrome. *(More information)*
- Vitamin B_6 is found in a variety of foods, including fish, poultry, nuts, legumes, potatoes, and bananas. *(More information)*
- Several medications, including anti-tuberculosis drugs, anti-parkinsonians, nonsteroidal anti-inflammatory drugs, and oral contraceptives, may interfere with vitamin B_6 metabolism. *(More information)*

Vitamin B_6 is a water-soluble vitamin that was first isolated in the 1930s. The term vitamin B_6 refers to six common forms, namely pyridoxal, pyridoxine (pyridoxol), pyridoxamine, and their phosphorylated forms. The phosphate ester derivative pyridoxal 5'-phosphate (PLP) is the bioactive coenzyme form involved in over 4% of all enzymatic reactions (**Figure 1**) (1-3).

Figure 1. Vitamin B_6 Chemical Structures



Non-phosphorylated forms of vitamin B_6 include pyridoxine, pyridoxal, and pyridoxamine. While all three of these variants can be phosphorylated, the phosphate ester derivative of pyridoxal, pyridoxal 5'-phosphate (PLP), is the cofactor of most vitamin B_6-dependent enzymes in the body.

Function

Vitamin B_6 must be obtained from the diet because humans cannot synthesize it. PLP plays a vital role in the function of over 100 enzymes that catalyze essential chemical reactions in the human body (4). PLP-dependent enzymes have been classified into five structural classes known as Fold Type I-V (5):

- Fold Type I - aspartate aminotransferase family
- Fold Type II - tryptophan synthase family
- Fold Type III - alanine racemase family
- Fold Type IV - D-amino acid aminotransferase family
- Fold Type V - glycogen phosphorylase family

The many biochemical reactions catalyzed by PLP-dependent enzymes are involved in essential biological processes, such as hemoglobin and amino acid biosynthesis, as well as fatty acid metabolism. Of note, PLP also functions as a coenzyme for glycogen phosphorylase, an enzyme that catalyzes the release of glucose from stored glycogen. Much of the PLP in the human body is found in muscle bound to glycogen phosphorylase. PLP is also a coenzyme for reactions that generate glucose from amino acids, a process known as gluconeogenesis (6).

Nervous system function

In the brain, the PLP-dependent enzyme aromatic L-amino acid decarboxylase catalyzes the synthesis of two major neurotransmitters: serotonin from the amino acid tryptophan and dopamine from L-3,4-dihydroxyphenylalanine (L-Dopa). Other neurotransmitters, including glycine, D-serine, glutamate, histamine, and γ-aminobutyric acid (GABA), are also synthesized in reactions catalyzed by PLP-dependent enzymes (7).

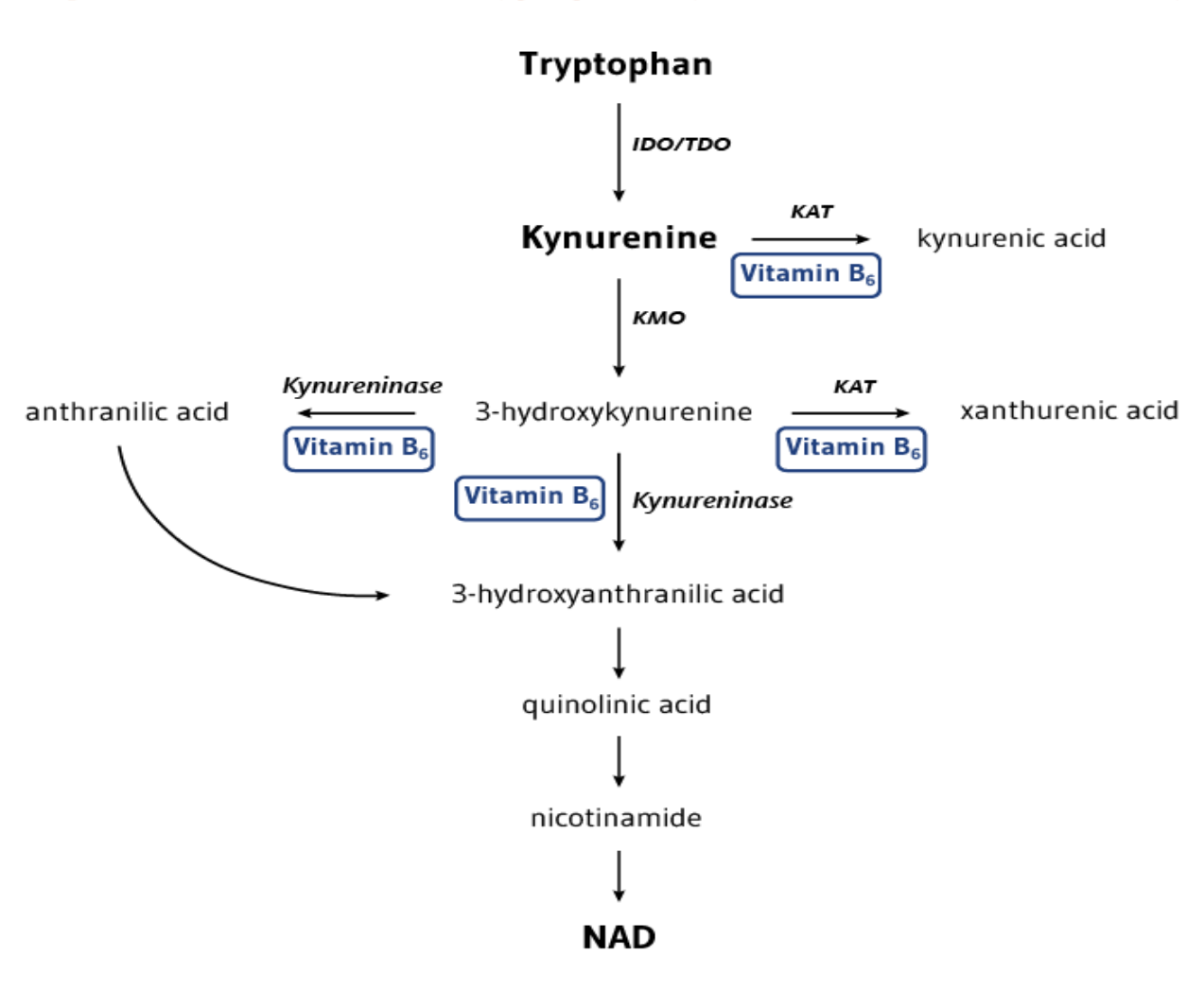
Hemoglobin synthesis and function

PLP functions as a coenzyme of 5-aminolevulinic acid synthase, which is involved in the synthesis of heme, an iron-containing component of hemoglobin. Hemoglobin is found in red blood cells and is critical to their ability to transport oxygen throughout the body. Both pyridoxal and PLP are able to bind to the hemoglobin molecule and affect its ability to pick up and release oxygen. However, the impact of this on normal oxygen delivery to tissues is not known (6, 8). Vitamin B_6 deficiency may impair hemoglobin synthesis and lead to microcytic anemia (3).

Tryptophan metabolism

Deficiency in another B vitamin, niacin, is easily prevented by adequate dietary intakes. The dietary requirement for niacin and the niacin coenzyme, nicotinamide adenine dinucleotide (NAD), can be also met, though to a fairly limited extent, by the catabolism of the essential amino acid tryptophan in the tryptophan-kynurenine pathway (**Figure 2**). Key reactions in this pathway are PLP-dependent; in particular, PLP is the cofactor for the enzyme kynureninase, which catalyzes the conversion of 3-hydroxykynurenine to 3-hydroxyanthranilic acid. A reduction in PLP availability appears to primarily affect kynureninase activity, limiting NAD production and leading to higher concentrations of kynurenine, 3-hydroxykynurenine, and xanthurenic acid in blood and urine (**Figure 2**) (9). Thus, while dietary vitamin B_6 restriction impairs NAD synthesis from tryptophan, adequate PLP levels help maintain NAD formation from tryptophan (10). The effect of vitamin B_6 inadequacy on immune activation and inflammation may be partly related to the role of PLP in the tryptophan-kynurenine metabolism (see Disease Prevention).

Figure 2. Overview of the Tryptophan-Kynurenine Metabolic Pathway



Pyridoxal 5'-phosphate, a vitamin B_6 coenzyme, is required for the activity of key enzymes in the tryptophan catabolic pathway, KAT and kynureninase. Dietary restriction in vitamin B_6 most prominently affects kynureninase activity and results in the shift from 3-hydroxykynurenine metabolism and NAD formation to the production of kynurenic acid and xanthurenic acid. *IDO, indoleamine 2,3-dioxygenase; KAT, kynurenine aminotransferase; KMO, kynurenine 3-monooxygenase; NAD, nicotinamide adenine dinucleotide; TDO, tryptophan 2,3-dioxygenase*

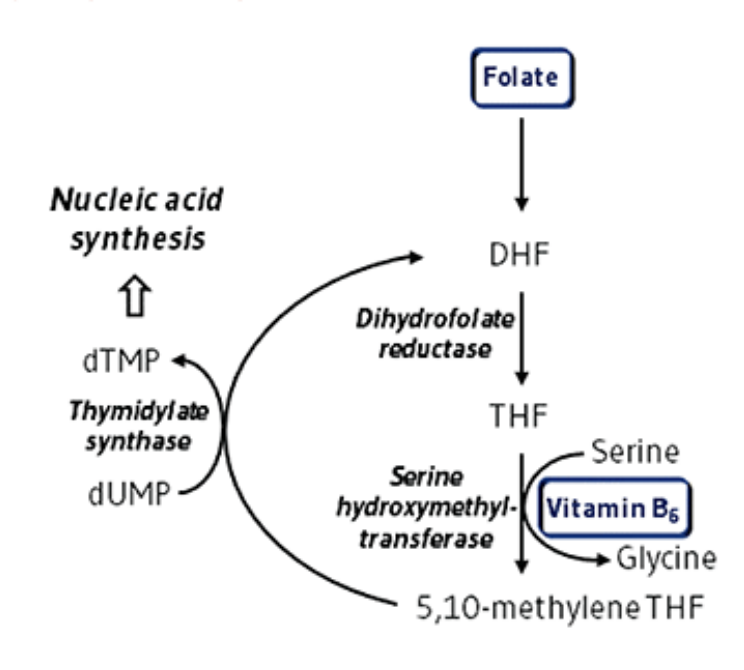
Hormone function

Steroid hormones, such as estrogen and testosterone, exert their effects in the body by binding to steroid hormone receptors in the nucleus of target cells. The nuclear receptors themselves bind to specific regulatory sequences in DNA and alter the transcription of target genes. Experimental studies have uncovered a mechanism by which PLP may affect the activity of steroid receptors and decrease their effects on gene expression. It was found that PLP could interact with RIP140/NRIP1, a repressor of nuclear receptors known for its role in reproductive biology (11). Yet, additional research is needed to confirm that this interaction can enhance RIP140/NRIP1 repressive activity on steroid receptor-mediated gene expression. If the activity of steroid receptors for estrogen, progesterone, testosterone, or other steroid hormones can be inhibited by PLP, it is possible that vitamin B_6 status may influence one's risk of developing diseases driven by steroid hormones, such as breast and prostate cancers (6).

Nucleic acid synthesis

The synthesis of nucleic acids from precursors thymidine and purines is dependent on folate coenzymes. The *de novo* thymidylate (dTMP) biosynthesis pathway involves three enzymes: dihydrofolate reductase (DHFR), serine hydroxymethyltransferase (SHMT), and thymidylate synthase (TYMS) (**Figure 3**). PLP serves as a coenzyme for SHMT, which catalyzes the simultaneous conversions of serine to glycine and tetrahydrofolate (THF) to 5,10-methylene THF. The latter molecule is the one-carbon donor for the generation of dTMP from deoxyuridine monophosphate (dUMP) by TYMS.

Figure 3. *De Novo* Thymidylate Biosynthesis



Folate coenzymes are essential intermediates in the synthesis of nucleic acid precursors thymidine and purines. Thymidylate biosynthesis pathway involves three enzymes: dihydrofolate reductase, serine hydroxymethyltransferase, and thymidylate synthase. Pyridoxal 5'-phosphate (PLP), a vitamin B_6 coenzyme, is required by serine hydroxymethyltransferase, which uses serine as a one-carbon donor for the generation of 5,10-methylenetetrahydrofolate (5,10-methylene THF) from THF. 5,10-methylene THF is then used in both methionine transmethylation cycle (not shown here) and thymidylate biosynthesis. *DHF, dihydrofolate; dUMP, deoxyuridine monophosphate; dTMP, deoxythymidine monophosphate (thymidylate); PLP, pyridoxal 5'-phosphate; THF, tetrahydrofolate.*

Deficiency

Severe deficiency of vitamin B_6 is uncommon. Alcoholics are thought to be most at risk of vitamin B_6 deficiency due to low dietary intakes and impaired metabolism of the vitamin. In the early 1950s, seizures were observed in infants as a result of severe vitamin B_6 deficiency caused by an error in the manufacture of infant formula (7). Abnormal electroencephalogram (EEG) patterns have also been reported in vitamin B_6-deficient adults. Other neurologic symptoms observed in severe vitamin B_6 deficiency include irritability, depression, and confusion; additional symptoms include inflammation of the tongue, sores or ulcers of the mouth, and ulcers of the skin at the corners of the mouth (12).

The Recommended Dietary Allowance (RDA)

Since vitamin B_6 is involved in many aspects of metabolism, especially in amino acid metabolic pathways, an individual's protein intake is likely to influence the requirement for vitamin B_6 (13). Unlike previous recommendations issued by the Food and Nutrition Board (FNB) of the Institute of Medicine, the most recent RDA for vitamin B_6 was not expressed in terms of protein intake, although the relationship was considered in setting the RDA (14). The current RDA was revised by the FNB in 1998 and is presented in **Table 1**.

Table 1. Recommended Dietary Allowance (RDA) for Vitamin B_6

Life Stage	Age	Males (mg/day)	Females (mg/day)
Infants	0-6 months	0.1 (AI)	0.1 (AI)
Infants	7-12 months	0.3 (AI)	0.3 (AI)
Children	1-3 years	0.5	0.5
Children	4-8 years	0.6	0.6
Children	9-13 years	1.0	1.0
Adolescents	14-18 years	1.3	1.2
Adults	19-50 years	1.3	1.3
Adults	51 years and older	1.7	1.5
Pregnancy	all ages	-	1.9
Breast-feeding	all ages	-	2.0

Disease Prevention

Immune dysfunction

Several enzymatic reactions in the tryptophan-kynurenine pathway are dependent on vitamin B_6 coenzyme, pyridoxal 5'-phosphate (PLP) (see **Figure 2** above) (see Tryptophan metabolism). This pathway is known to be activated during pro-inflammatory immune responses and plays a critical role in immune tolerance of the fetus during pregnancy (15). Key intermediates in the tryptophan-kynurenine pathway are involved in the regulation of immune responses. Several tryptophan derivatives have been found to induce the death (apoptosis) or block the proliferation of certain types of immune cells, such as lymphocytes (in particular T-helper 1). They can also inhibit the production of pro-inflammatory cytokines (reviewed in 15). There is evidence to suggest that adequate vitamin B_6 intake is important for optimal immune system function, especially in older individuals (16, 17). Yet, chronic inflammation that triggers tryptophan degradation and underlies many diseases (e.g., cardiovascular disease and cancers) may precipitate the loss of PLP and increase vitamin B_6 requirements. Additional research is needed to evaluate whether vitamin B_6 intakes higher than the current RDA could prevent and/or reverse immune system impairments (see also Vitamin B_6 and inflammation).

Cardiovascular disease

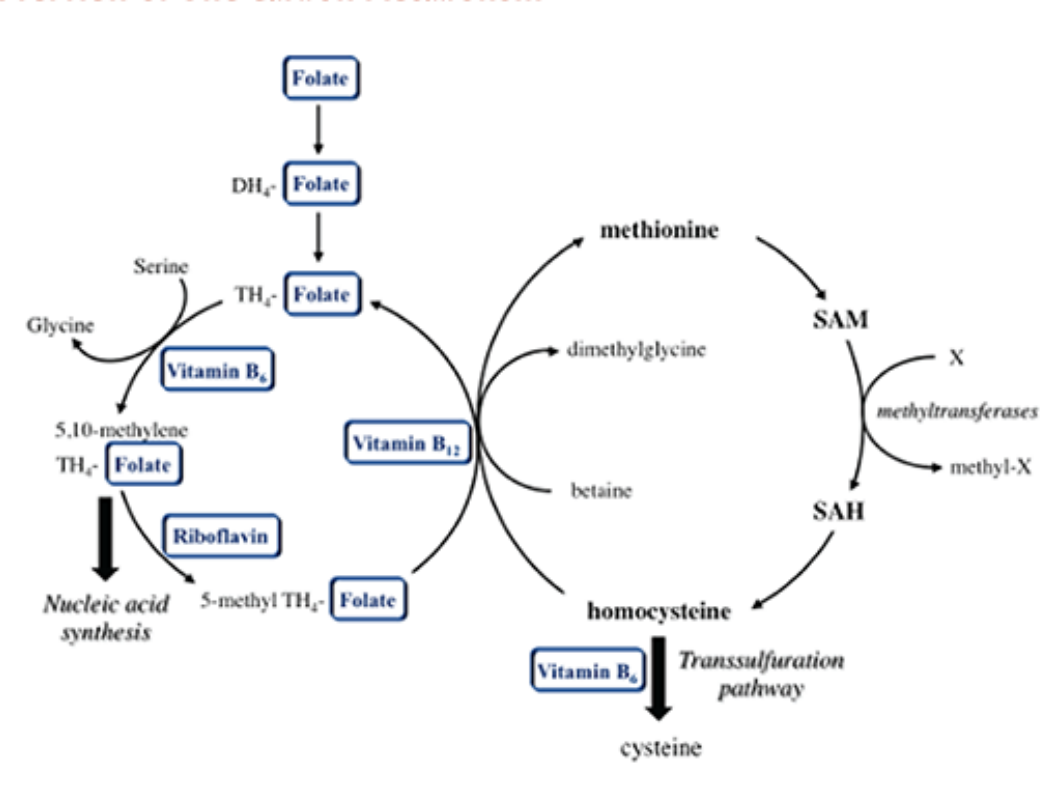
The use of multivitamin supplements (including vitamin B_6) has been associated with a 24% lower risk of incidental coronary artery disease (CAD) in a large prospective study of 80,082 women from the US Nurses' Health Study cohort (18). Using food frequency questionnaires, the authors observed that women in the highest quintile of vitamin B_6 intakes from both food and supplements (median, 4.6 mg/day) had a 34% lower risk of CAD compared to those in the lowest quintile (median, 1.1 mg/day). CAD is characterized by the abnormal stenosis (narrowing) of coronary arteries (generally due to atherosclerosis), which can result in a potentially fatal myocardial infarction (heart attack). More recently, a prospective study that followed a Japanese cohort of over 40,000 middle-aged individuals for 11.5 years reported a 48% lower risk of myocardial infarction in those in the highest (mean, 1.6 mg/day) versus lowest quintile (mean, 1.3 mg/day) of vitamin B_6 intakes in non-supplement users (19).

Early observational studies have also demonstrated an association between suboptimal pyridoxal 5'-phosphate (PLP) plasma level, elevated homocysteine blood level, and increased risk of cardiovascular disease (20-22). More recent research has confirmed that low plasma PLP status is a risk factor for CAD. In a case-control study, which included 184 participants with CAD and 516 healthy controls, low plasma PLP levels (<30 nanomoles/liter) were associated with a near doubling of CAD risk when compared to higher PLP levels (≥30 nanomoles/liter) (23). In a nested case-control study based on the Nurses' Health Study cohort and including 144 cases of myocardial infarction (of which 21 were fatal), women in the highest quartile of blood PLP levels (≥70 nanomoles/liter) had a 79% lower risk of myocardial infarction compared to those in the lowest quartile (<27.9 nanomoles/liter) (24).

Vitamin B_6 and homocysteine

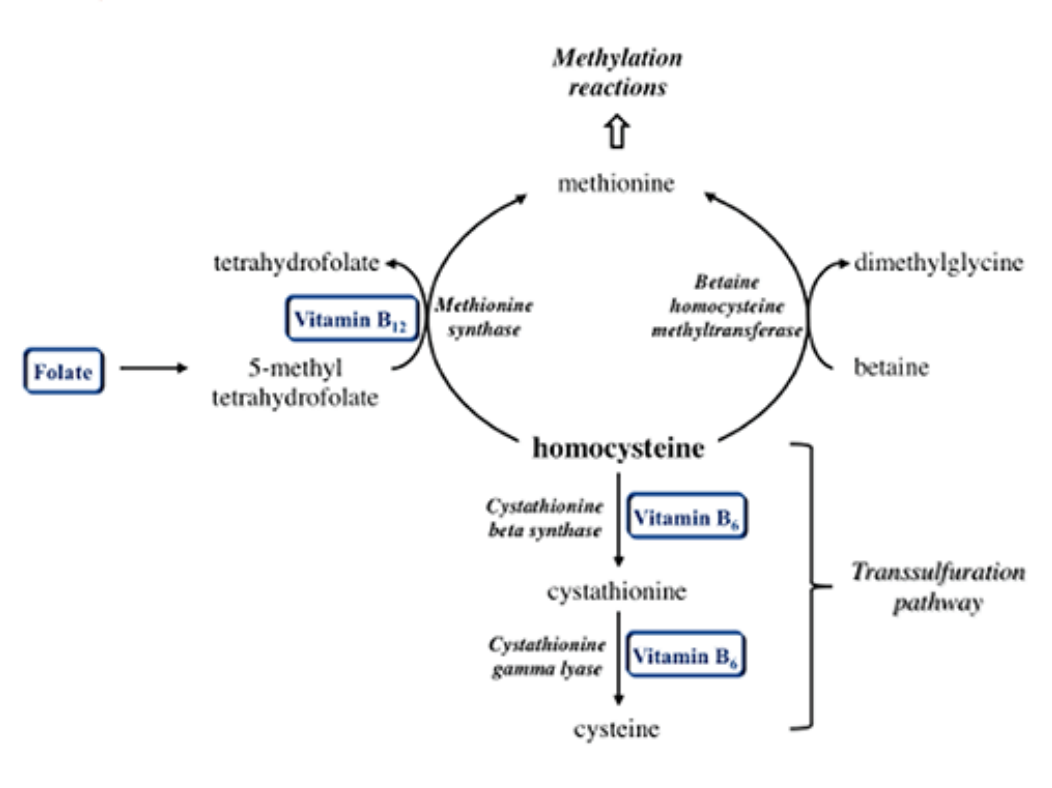
Even moderately elevated levels of homocysteine in the blood have been associated with increased risk for cardiovascular disease (CVD), including cardiac insufficiency (heart failure), CAD, myocardial infarction, and cerebrovascular attack (stroke) (25). During protein digestion, amino acids, including methionine, are released. Methionine is an essential amino acid and precursor of S-adenosylmethionine (SAM), the universal methyl donor for most methylation reactions, including the methylation of DNA, RNA, proteins, and phospholipids (**Figure 4**). Homocysteine is an intermediate in the metabolism of methionine. Healthy individuals utilize two different pathways to regenerate methionine from homocysteine in the methionine remethylation cycle (**Figure 5**). One pathway relies on the vitamin B_{12}-dependent methionine synthase and the methyl donor, 5-methyl tetrahydrofolate (a folate derivative), to convert homocysteine back to methionine. The other reaction is catalyzed by betaine homocysteine methyltransferase, which uses betaine as a source of methyl groups for the formation of methionine from homocysteine. Moreover, two PLP-dependent enzymes are required to convert homocysteine to the amino acid cysteine in homocysteine transsulfuration pathway: cystathionine β synthase and cystathionine γ lyase (**Figure 5**). Thus, the amount of homocysteine in the blood may be influenced by nutritional status of at least three B vitamins, namely folate, vitamin B_{12}, and vitamin B_6.

Figure 4. Overview of One-carbon Metabolism



SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; TH4-folate, tetrahydrofolate.

Figure 5. Homocysteine Metabolism



Homocysteine is methylated to form the essential amino acid methionine in two pathways. The reaction of homocysteine remethylation catalyzed by the vitamin B_{12}-dependent methionine synthase captures a methyl group from the folate-dependent one-carbon pool (5-methyl tetrahydrofolate). A second pathway requires betaine (N,N,N-trimethylglycine) as a methyl donor for the methylation of homocysteine catalyzed by betaine homocysteine methyltransferase. The catabolic pathway of homocysteine, known as transsulfuration pathway, converts homocysteine to the amino acid cysteine via two vitamin B_6 (PLP)-dependent enzymes: cystathionine β synthase catalyzes the condensation of homocysteine with serine to form cystathionine, and cystathionine is then converted to cysteine, α-ketobutyrate, and ammonia by cystathionine γ lyase.

Deficiencies in one or all of these B vitamins may affect both remethylation and transsulfuration processes and result in abnormally elevated homocysteine levels. An early study found that vitamin B_6 supplementation could lower blood homocysteine levels after an oral dose of methionine was given (i.e., a methionine load test) (26), but vitamin B_6 supplementation might not be effective in decreasing fasting levels of homocysteine. In a recent study conducted in nine healthy young volunteers, the rise of homocysteine during the postprandial period (after a meal) was found to be greater with marginal vitamin B_6 deficiency (mean plasma PLP level of 19 nanomoles/liter) as compared to vitamin B_6 sufficiency (mean PLP level of 49 nanomoles/liter) (27). The authors reported an increased rate of cystathionine synthesis with vitamin B_6 restriction, suggesting that homocysteine catabolism in the transsulfuration may be maintained or enhanced in response to a marginal reduction in PLP availability. Yet, the flux ratio between methionine cycle and transsulfuration pathway appeared to favor homocysteine clearance by remethylation rather than transsulfuration in six out of nine participants (27).

Numerous randomized controlled trials, many in subjects with existing hyperhomocysteinemia and vascular dysfunction, have demonstrated that supplementation with folic acid, alone or combined with vitamin B_6 and vitamin B_{12}, could effectively reduce fasting plasma homocysteine concentrations. In 19 intervention studies recently included in a meta-analysis, reductions in homocysteine level in the blood following B-vitamin supplementation ranged between 7.6% and 51.7% compared to baseline levels (28). In contrast, studies supplementing individuals with only vitamin B_6 have usually failed to show an effect on fasting levels of homocysteine (29, 30). Of the three supplemental B vitamins, folic acid appears to be the main determinant in the regulation of fasting homocysteine levels when there is no coexisting deficiency of vitamin B_{12} or vitamin B_6 (31). Yet, the effect of homocysteine lowering on CVD risk reduction is debated. A recent meta-analysis of nine randomized controlled trials reported a 10% reduction in stroke events with supplemental B vitamins, with greater benefits for high-risk subjects (e.g., those with kidney disease) (32). However, most systematic reviews and meta-analyses of B-vitamin intervention studies to date have indicated a lack of causality between the decrease of fasting homocysteine levels and the prevention of cardiovascular events (28, 33-35). Moreover, B-vitamin supplementation trials in high-risk subjects have not resulted in significant changes in carotid intima-media thickness (CIMT) and flow-mediated dilation (FMD) of the brachial artery, two markers of vascular health used to assess atherosclerotic progression (36). Finally, in the Western Norway B Vitamin Intervention Trial (WENBIT), a randomized, double-blind, placebo-controlled trial in 87 subjects with suspected CAD, vitamin B_6 supplementation (40 mg/day of pyridoxine) for a median of 10 months had no effect on coronary stenosis progression, assessed by quantitative angiography (37).

It has been suggested that antiplatelet therapy used in the primary prevention of CVD might interfere with the effect of homocysteine lowering by B vitamins on CVD risk (38). In this context, a post-hoc subgroup analysis of the multicenter, randomized, double blind, placebo-controlled VITATOPS trial (39) proposed that the small benefit of homocysteine-lowering by B vitamins might be cancelled in patients treated with antiplatelet drugs (40). Yet, the benefit of B-vitamin supplementation in primary prevention (i.e., in non-antiplatelet users) remains to be established.

Vitamin B_6 and inflammation

A growing body of evidence currently suggests that low vitamin B_6 status may increase the risk of cardiovascular disease through mechanisms independent of homocysteine lowering (41-43). Markers of immune activation and inflammation have been associated with hyperhomocysteinemia (homocysteine levels >15 micromoles/liter) in individuals with coronary artery disease (CAD) (44). In fact, inflammation is involved in the early steps of atherosclerosis in which lipids deposit in plaques (known as atheromas) within arterial walls and increase the risk of CAD (45). In a case-control study that included 267 patients with CAD and 475 healthy controls, plasma PLP concentrations were inversely correlated with the levels of two markers of systemic inflammation, C-reactive protein (CRP) and fibrinogen (46). Yet, the study suggested that suboptimal PLP levels (<36.3 nanomoles/liter) might contribute to an increased risk of CAD independently of inflammation since the risk was unchanged after adjustment for inflammation markers (unadjusted odds ratio (OR): 1.71 vs. multivariate adjusted OR: 1.73). Furthermore, the analysis of inflammation markers in 2,686 participants of the US National Health and Nutrition Examination Survey (NHANES) 2003-2004 indicated that serum CRP concentrations were inversely related to total vitamin B_6 intakes (from both food and supplements). Specifically, the risk of having serum CRP levels greater than 10 mg/L (corresponding to high inflammatory activity) was 57% higher in individuals with vitamin B_6 intakes lower than 2 mg/day compared to those with intakes equal to and above 5 mg/day (41). In addition, the prevalence of inadequate vitamin B_6 status (plasma PLP levels <20 nanomoles/liter) with intakes lower than 5 mg/day was systematically greater in individuals with high versus low serum CRP concentrations (>10 mg/L vs. ≤3 mg/L), suggesting that inflammation might impair vitamin B_6 metabolism. These observations were confirmed in the study of another cohort (Framingham Offspring Study) in which vitamin B_6 status was linked to an overall inflammatory score based on the levels of 13 inflammation markers (including CRP, fibrinogen, tumor necrosis factor-α, and interleukin-6) (42). Specifically, plasma PLP levels were 24% lower in individuals in the highest versus lowest tertile of inflammatory score. Moreover, the inverse correlation between PLP levels and inflammatory scores remained significant regardless of vitamin B_6 intakes, questioning again the nature of this relationship. Interestingly, a recent analysis of data collected in the WENBIT study demonstrated that systemic inflammation was associated with an increased degradation of pyridoxal (PL) to 4-pyridoxic acid (PA), supporting the use of the ratio PA:(PL+PLP) as a marker of both vitamin B_6 status and systemic inflammation (47). Finally, while inflammation may contribute to lower vitamin B_6 status, current evidence fails to support a role for vitamin B_6 in the control of inflammation in patients with cardiovascular disease (48, 49).

Cognitive decline and Alzheimer's disease

A few observational studies have linked cognitive decline and Alzheimer's disease (AD) in the elderly with inadequate status of folate, vitamin B_{12}, and vitamin B_6 (50). Yet, the relationship between B vitamins and cognitive health in aging is complicated by both the high prevalence of hyperhomocysteinemia and signs of systemic inflammation in elderly people (51). On the one hand, since inflammation may impair vitamin B_6 metabolism, low serum PLP levels may well be caused by processes related to aging rather than by malnutrition. On the other hand, high serum homocysteine may possibly be a risk factor for cognitive decline in the elderly, although the matter remains under debate. Specifically, the meta-analysis of 19 randomized, placebo-controlled trials of B-vitamin supplementation failed to report any difference in several measures of cognitive function between treatment and placebo groups, despite the treatment effectively lowering homocysteine levels (52). In a recent randomized, double-blind, placebo-controlled study of 2,695 stroke survivors with or without cognitive impairments, daily supplementation with 2 mg of folic acid, 0.5 mg of vitamin B_{12}, and 25 mg of vitamin B_6 for 3.4 years resulted in significant reductions in mean homocysteine levels (by 28% and 43% in cognitively unimpaired and impaired patients, respectively) compared to placebo. Yet, the B-vitamin intervention had no effect on either the incidence of newly diagnosed cognitive impairments or on measures of cognitive performance when compared to placebo (53). In contrast, another recent placebo-controlled trial found that a daily B-vitamin regimen that led to significant homocysteine lowering in high-risk elderly individuals could limit the progressive atrophy of gray matter brain regions associated with the AD process (54). Yet, the authors attributed the changes in homocysteine levels primarily to vitamin B_{12}. Because of mixed findings, it is presently unclear whether supplementation with B vitamins might blunt cognitive decline in the elderly. Evidence is needed to determine whether marginal B-vitamin deficiencies, which are relatively common in the elderly, even contribute to age-associated declines in cognitive function, or whether both result from processes associated with aging and/or disease.

Depression

Late-life depression is a common disorder sometimes occurring after acute illnesses, such as hip fracture or stroke (55, 56). Coexistence of symptoms of depression and low vitamin B_6 status (plasma PLP level ≤20 nanomoles/liter) has been reported in a few cross-sectional studies (57, 58). In a prospective study of 3,503 free-living people aged 65 and older from the Chicago Health and Aging Project, total vitamin B_6 intakes (but not dietary intakes alone) were inversely correlated with the incidence of depressive symptoms during a mean follow-up period of 7.2 years (59). In a randomized, double-blind, placebo-controlled trial in 563 individuals who suffered from a recent stroke, daily supplementation of 2 mg of folic acid, 0.5 mg of vitamin B_{12}, and 25 mg of vitamin B_6 halved the risk of developing a major depressive episode during a mean follow-up period of 7.1 years (60). This reduction in risk was associated with a 25% lower level of plasma homocysteine in supplemented patients compared to controls. Additional evidence is needed to evaluate whether B vitamins could be included in the routine management of older people at high risk for depression.

Cancer

Chronic inflammation that underlies most cancers may enhance vitamin B_6 degradation (see Vitamin B_6 and inflammation). In addition, because PLP is required for the methionine cycle, homocysteine catabolism, and thymidylate synthesis, low vitamin B_6 status might affect these pathways and potentially increase the risk for chronic conditions. The systematic review of nine prospective studies found either inverse or positive associations between vitamin B_6 intakes and colorectal cancer (CRC) risk (61). Inconsistent evidence regarding the link between vitamin B_6 intakes and breast cancer was also recently reported in a meta-analysis (62). Yet, a prospective study that followed nearly 500,000 older adults for nine years observed that the risk of esophageal and stomach cancers was lower in participants in the highest versus lowest quintile of total vitamin B_6 intakes (median values, 2.7 mg/day vs. 1.4 mg/day) (63). Additionally, a meta-analysis of four nested case-control studies reported a 48% reduction in CRC risk in the highest versus lowest quartile of blood PLP level (61). Another meta-analysis of five nested case-control studies found higher versus lower serum PLP levels to be associated with a 29% lower risk of breast cancer in postmenopausal, but not premenopausal, women (62).

Very few randomized, placebo-controlled trials investigating the nature of the association between B vitamins and cancer risk have focused on vitamin B_6. Two earlier studies conducted in subjects with coronary artery disease failed to observe any benefit of supplemental vitamin B_6 (40 mg/day) on CRC risk and mortality (reviewed in 64). A recent randomized, double-blind, placebo-controlled study conducted in 1,470 women with high cardiovascular risk showed that daily supplementation with 2.5 mg of folic acid, 1 mg of vitamin B_{12}, and 50 mg of vitamin B_6 for a mean treatment period of 7.3 years had no effect on the risk of developing colorectal adenoma when compared to placebo (65).

Kidney stones

A large prospective study examined the relationship between vitamin B_6 intake and the occurrence of symptomatic kidney stones in women. A group of more than 85,000 women without a prior history of kidney stones were followed over 14 years, and those who consumed 40 mg or more of vitamin B_6 daily had only two-thirds the risk of developing kidney stones compared with those who consumed 3 mg or less (66). However, in a group of more than 45,000 men followed for 14 years, no association was found between vitamin B_6 intake and the occurrence of kidney stones (67). Limited experimental data have suggested that supplementation with high doses of pyridoxamine may help decrease the formation of calcium oxalate kidney stones and reduce urinary oxalate levels, an important determinant of calcium oxalate kidney stone formation (68, 69). Presently, the relationship between vitamin B_6 intake and the risk of developing kidney stones requires further study before any recommendations can be made.

Disease Treatment

Vitamin B_6 supplements at pharmacologic doses (i.e., doses much larger than those needed to prevent deficiency) have been used in an attempt to treat a wide variety of conditions, some of which are discussed below.

Metabolic diseases

A few rare inborn metabolic disorders, including pyridoxine-dependent epilepsy (PDE) and pyridoxamine 5'-phosphate oxidase (PNPO) deficiency, are the cause of early-onset epileptic encephalopathies that are found to be responsive to pharmacologic doses of vitamin B_6. In individuals affected by PDE and PNPO deficiency, PLP bioavailability is limited, and treatment with pyridoxine and/or PLP have been used to alleviate or abolish epileptic seizures characterizing these conditions (70, 71). Pyridoxine therapy, along with dietary protein restriction, is also used in the management of vitamin B_6 responsive homocystinuria caused by the deficiency of the PLP-dependent enzyme, cystathionine β synthase (72).

Morning sickness

Nausea and vomiting in pregnancy (NVP), often referred to as morning sickness, can affect up to 85% of women during early pregnancy and usually lasts between 12 and 16 weeks (73). Vitamin B_6 has been used since the 1940s to treat nausea during pregnancy. Vitamin B_6 was originally included in the medication Bendectin, which was prescribed for NVP treatment and later withdrawn from the market due to unproven concerns that it increased the risk for birth defects. Vitamin B_6 itself is considered safe during pregnancy and has been used in pregnant women without any evidence of fetal harm (74). The results of two double-blind, placebo-controlled trials, including 401 pregnant women that used 25 mg of pyridoxine every eight hours for three days (75) or 10 mg of pyridoxine every eight hours for five days (76), suggested that vitamin B_6 may be beneficial in reducing nausea. A recent systematic review of randomized controlled trials on NVP symptoms during early pregnancy found supplemental vitamin B_6 to be somewhat effective (77). It should be noted that NVP usually resolves without any treatment, making it difficult to perform well-controlled trials. More recently, NVP symptoms were evaluated using Pregnancy Unique Quantification of Emesis (PUQE) scores in a randomized, double-blind, placebo-controlled study conducted in 256 pregnant women (7-14 weeks' gestation) suffering from NVP (78). Supplementation with pyridoxine and the drug doxylamine significantly improved NVP symptoms, as assessed by lower PUQE scores compared to placebo. Moreover, more women supplemented with pyridoxine-doxylamine (48.9%) than placebo-treated (32.8%) asked to continue their treatment at the end of the 15-day trial. The American and Canadian Colleges of Obstetrics and Gynecology have recommended the use of vitamin B_6 (pyridoxine hydrochloride, 10 mg) and doxylamine succinate (10 mg) as first-line therapy for NVP (73).

Premenstrual syndrome

Premenstrual syndrome (PMS) refers to a cluster of symptoms, including but not limited to fatigue, irritability, moodiness/depression, fluid retention, and breast tenderness, that begin sometime after ovulation (mid-cycle) and subside with the onset of menstruation (the monthly period). A systematic review and meta-analysis of nine randomized, placebo-controlled trials suggested that supplemental vitamin B_6, up to 100 mg/day, may be of value to treat PMS, including mood symptoms; however, only limited conclusions could be drawn because most of the studies were of poor quality (79). Another more recent review of 13 randomized controlled studies also emphasized the need for conclusive evidence before recommendations can be made (80).

Depression

The importance of PLP-dependent enzymes in the synthesis of several neurotransmitters (see Nervous system function) has led researchers to consider whether vitamin B_6 deficiency may contribute to the onset of depressive symptoms (see Disease Prevention). There is limited evidence suggesting that supplemental vitamin B_6 may have therapeutic efficacy in the management of depression. In a randomized, placebo-controlled trial conducted in 225 elderly patients hospitalized for acute illness, a six-month intervention with daily multivitamin/mineral supplements improved nutritional B-vitamin status and decreased the number and severity of depressive symptoms when compared to placebo (81). In addition, while supplement intake effectively reduced plasma homocysteine levels compared to placebo, the effect of supplementation on depressive symptoms at the end of the trial was greater in treated subjects in the lowest versus highest quartile of homocysteine levels (≤10 micromoles/liter vs. ≥16.1 micromoles/liter) (82). Yet, the etiology of late-onset depression is unclear and evidence is currently lacking to suggest whether supplemental B vitamins (including vitamin B_6) could relieve depressive symptoms.

Carpal tunnel syndrome

Carpal tunnel syndrome (CTS) causes numbness, pain, and weakness of the hand and fingers due to compression of the median nerve at the wrist. It may result from repetitive stress injury of the wrist or from soft-tissue swelling, which sometimes occurs with pregnancy or hypothyroidism. Early studies by the same investigator suggested that supplementation with 100-200 mg/day of vitamin B_6 for several months might improve CTS symptoms in individuals with low vitamin B_6 status (83, 84). In addition, a cross-sectional study in 137 men not taking vitamin supplements found that decreased blood levels of PLP were associated with increased pain, tingling, and nocturnal awakening—all symptoms of CTS (85). However, studies using electrophysiological measurements of median nerve conduction have largely failed to find an association between vitamin B_6 deficiency and CTS (86). While a few studies have noted some symptomatic relief with vitamin B_6 supplementation, double-blind, placebo-controlled trials have not generally found vitamin B_6 to be effective in treating CTS (86). Yet, despite its equivocal effectiveness, vitamin B_6 supplementation is sometimes used in complementary therapy in an attempt to avoid hand surgery. Patients taking high doses of vitamin B_6 should be advised by a physician and monitored for vitamin B_6-related toxicity symptoms (see Toxicity) (87).

Sources

Food sources

The analysis of data collected in the US NHANES 2003-2004 has indicated that vitamin B_6 intakes from food only averaged about 1.9 mg/day (88). Yet, despite values well above the current RDA, total vitamin B_6 intakes (combining food and supplements) below 2 mg/day appear to be associated with relatively high proportions of low vitamin B_6 status in all age groups (see Supplements). Many plant foods contain a unique form of vitamin B_6 called pyridoxine glucoside; this form of vitamin B_6 appears to be only about half as bioavailable as vitamin B_6 from other food sources or supplements (7). Vitamin B_6 in a mixed diet has been found to be approximately 75% bioavailable (14). In most cases, including foods in the diet that are rich in vitamin B_6 should supply enough to meet the current RDA. However, those who follow a very restricted vegetarian diet might need to increase their vitamin B_6 intake by eating foods fortified with vitamin B_6 or by taking a supplement. Some foods that are relatively rich in vitamin B_6 and their vitamin B_6 content in milligrams (mg) are listed in **Table 2**. For more information on the nutrient content of specific foods, search USDA's FoodData Central.

Table 2. Some Food Sources of Vitamin B_6

Food	Serving	Vitamin B_6 (mg)
Fortified breakfast cereal	1 cup	0.5-2.5
Salmon, wild (cooked)	3 ounces*	0.48-0.80
Potato, Russet, with skin (baked)	1 medium	0.70
Turkey, light meat (cooked)	3 ounces	0.69
Avocado	1 medium	0.52
Chicken, light meat without skin (cooked)	3 ounces	0.51
Spinach (cooked)	1 cup	0.44
Banana	1 medium	0.43
Dried plums, pitted	1 cup	0.36
Hazelnuts (dry roasted)	1 ounce	0.18
Vegetable juice cocktail	6 ounces	0.13
*A three-ounce serving of meat or fish is about the size of a deck of cards.		

Supplements

Vitamin B_6 is available as pyridoxine hydrochloride in multivitamin, vitamin B-complex, and vitamin B_6 supplements (89). In NHANES 2003-2004, low vitamin B_6 status (plasma PLP level <20 nanomoles/liter) was reported in 24% of non users of supplements and 11% of supplement users. Moreover, total vitamin B_6 intakes (from food and supplements) lower than 2 mg/day were associated with high proportions of low plasma PLP levels: 16% in men aged 13-54 years, 24% in menstruating women, and 26% in individuals aged 65 years and older. Finally, the prevalence of low PLP levels was found to be greater in individuals consuming less than 2 mg/day of vitamin B_6 compared to higher intakes. For example, only 14% of men and women aged 65 and older had low PLP values with total vitamin B_6 intakes of 2-2.9 mg/day compared to 26% in those consuming less than 2 mg/day of vitamin B_6 (88).

Safety

Toxicity

Because adverse effects have only been documented from vitamin B_6 supplements and never from food sources, safety concerning only the supplemental form of vitamin B_6 (pyridoxine) is discussed. Although vitamin B_6 is a water-soluble vitamin and is excreted in the urine, long-term supplementation with very high doses of pyridoxine may result in painful neurological symptoms known as sensory neuropathy. Symptoms include pain and numbness of the extremities and in severe cases, difficulty walking. Sensory neuropathy typically develops at doses of pyridoxine in excess of 1,000 mg per day. However, there have been a few case reports of individuals who developed sensory neuropathies at doses of less than 500 mg daily over a period of months. Yet, none of the studies in which an objective neurological examination was performed reported evidence of sensory nerve damage at intakes below 200 mg pyridoxine daily (90). To prevent sensory neuropathy in virtually all individuals, the Food and Nutrition Board of the Institute of Medicine set the tolerable upper intake level (UL) for pyridoxine at 100 mg/day for adults (**Table 3**) (14). Because placebo-controlled studies have generally failed to show therapeutic benefits of high doses of pyridoxine, there is little reason to exceed the UL of 100 mg/day.

Table 3. Tolerable Upper Intake Level (UL) for Vitamin B_6

Age Group	UL (mg/day)
Infants 0-12 months	Not possible to establish*
Children 1-3 years	30
Children 4-8 years	40
Children 9-13 years	60
Adolescents 14-18 years	80
Adults 19 years and older	100
*Source of intake should be from food and formula only.	

Drug interactions

Certain medications interfere with the metabolism of vitamin B_6; therefore, some individuals may be vulnerable to a vitamin B_6 deficiency if supplemental vitamin B_6 is not taken. In the NHANES 2003-2004 analysis, significantly more current and past users of oral contraceptives (OCs) among menstruating women had low plasma PLP levels compared to women who have never used OCs, suggesting that the estrogen content of OCs may interfere with vitamin B_6 metabolism (see Side effects of oral contraceptives) (88). Anti-tuberculosis medications (e.g., isoniazid and cycloserine), the metal chelator penicillamine, and anti-parkinsonian drugs like L-Dopa can all form complexes with vitamin B_6 and limit its bioavailability, thus creating a functional deficiency. PLP bioavailability may also be reduced by methylxanthines, such as theophylline used to treat certain respiratory conditions (7). The long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs; e.g. celecoxib and naproxen) may also impair vitamin B_6 metabolism (91). Conversely, high doses of vitamin B_6 have been found to decrease the efficacy of two anticonvulsants, phenobarbital and phenytoin, and of L-Dopa (6, 90).

Side effects of oral contraceptives

Because vitamin B_6 is required for the metabolism of the amino acid tryptophan, the tryptophan load test (an assay of tryptophan metabolites after an oral dose of tryptophan) has been used as a functional assessment of vitamin B_6 status. Abnormal tryptophan load tests in women taking high-dose oral contraceptives (OCs) in the 1960s and 1970s suggested that these women were vitamin B_6 deficient, which led to the prescription of high doses of vitamin B_6 (100-150 mg/day) to women taking OCs. However, most other indices of vitamin B_6 status were normal in women on high-dose OCs, and the estrogen content of OCs appeared to be more likely responsible for the abnormality in tryptophan metabolism (88). Yet, more recently, the use of lower dose formulations has also been associated with vitamin B_6 inadequacy (88, 92). Although it is not known whether OCs actually impair vitamin B_6 metabolism or merely affect the tissue distribution of PLP, the use of OCs may place women at higher risk of vitamin B_6 deficiency when they discontinue OCs and become pregnant (93). Whether OC users are at higher risk of cardiovascular disease despite normal homocysteine levels also needs to be determined. Finally, although high doses of vitamin B_6 (pyridoxine) have demonstrated no benefit in preventing the risk of side effects from OCs (94), the use of vitamin B_6 supplements may be warranted in current and past OC users.

Linus Pauling Institute Recommendation

The Linus Pauling Institute supports the RDA for vitamin B_6. LPI recommends that all adults take a daily multivitamin/mineral supplement, which usually contains at least 2 mg of vitamin B_6. This amount is slightly above the RDA but still 50 times lower than the tolerable upper intake level (UL) set by the Food and Nutrition Board (see Safety).

Older adults (>50 years)

Early metabolic studies have indicated that the requirement for vitamin B_6 in older adults is approximately 2 mg daily (95). Yet, the analysis of the US population survey (NHANES) 2003-2004 showed that adequate vitamin B_6 status and low homocysteine levels were associated with total vitamin B_6 intakes equal to and above 3 mg/day in people aged 65 years and older (88). The Linus Pauling Institute recommends that older adults take a multivitamin/mineral supplement, which provides at least 2.0 mg of vitamin B_6 daily.

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Vitamin B12

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Summary

- Vitamin B_{12} or cobalamin plays essential roles in folate metabolism and in the synthesis of the citric acid cycle intermediate, succinyl-CoA. *(More information)*
- Vitamin B_{12} deficiency is commonly associated with chronic stomach inflammation, which may contribute to an autoimmune vitamin B_{12} malabsorption syndrome called pernicious anemia and to a food-bound vitamin B_{12} malabsorption syndrome. Impairment of vitamin B_{12} absorption can cause megaloblastic anemia and neurologic disorders in deficient subjects. *(More information)*
- Normal function of the digestive system required for food-bound vitamin B_{12} absorption is commonly impaired in individuals over 60 years of age, placing them at risk for vitamin B_{12} deficiency. *(More information)*
- Vitamin B_{12} and folate are important for homocysteine metabolism. Elevated homocysteine levels in blood are a risk factor for cardiovascular disease (CVD). Although B vitamin supplementation has been proven effective to control homocysteine levels, current data from intervention trials have not shown that lowering homocysteine levels decreases CVD risk. *(More information)*
- The preservation of DNA integrity is dependent on folate and vitamin B_{12} availability. Poor vitamin B_{12} status has been linked to increased risk of breast cancer in some, but not all, observational studies. There is a need to evaluate whether supplemental vitamin B_{12}, along with folic acid, could help reduce breast cancer incidence. *(More information)*
- Low maternal vitamin B_{12} status has been associated with an increased risk of neural tube defects (NTD), but it is not known whether vitamin B_{12} supplementation could help reduce the risk of NTD. *(More information)*
- Vitamin B_{12} is essential for the preservation of the myelin sheath around neurons and for the synthesis of neurotransmitters. While hyperhomocysteinemia may increase the risk of cognitive impairment, it is not clear whether vitamin B_{12} deficiency contributes to the risk of dementia in the elderly. Although B-vitamin supplementation lowers homocysteine levels in older subjects, the long-term benefit is not yet known. *(More information)*
- Both depression and osteoporosis have been linked to diminished vitamin B_{12} status and high homocysteine levels. *(More information)*
- Products of animal origin constitute the primary source of vitamin B_{12}. Older individuals and vegans are advised to use vitamin B_{12} fortified foods and supplements to meet their needs. *(More information)*
- The long-term use of certain medications, such as inhibitors of stomach acid secretion, can adversely affect vitamin B_{12} absorption. *(More information)*

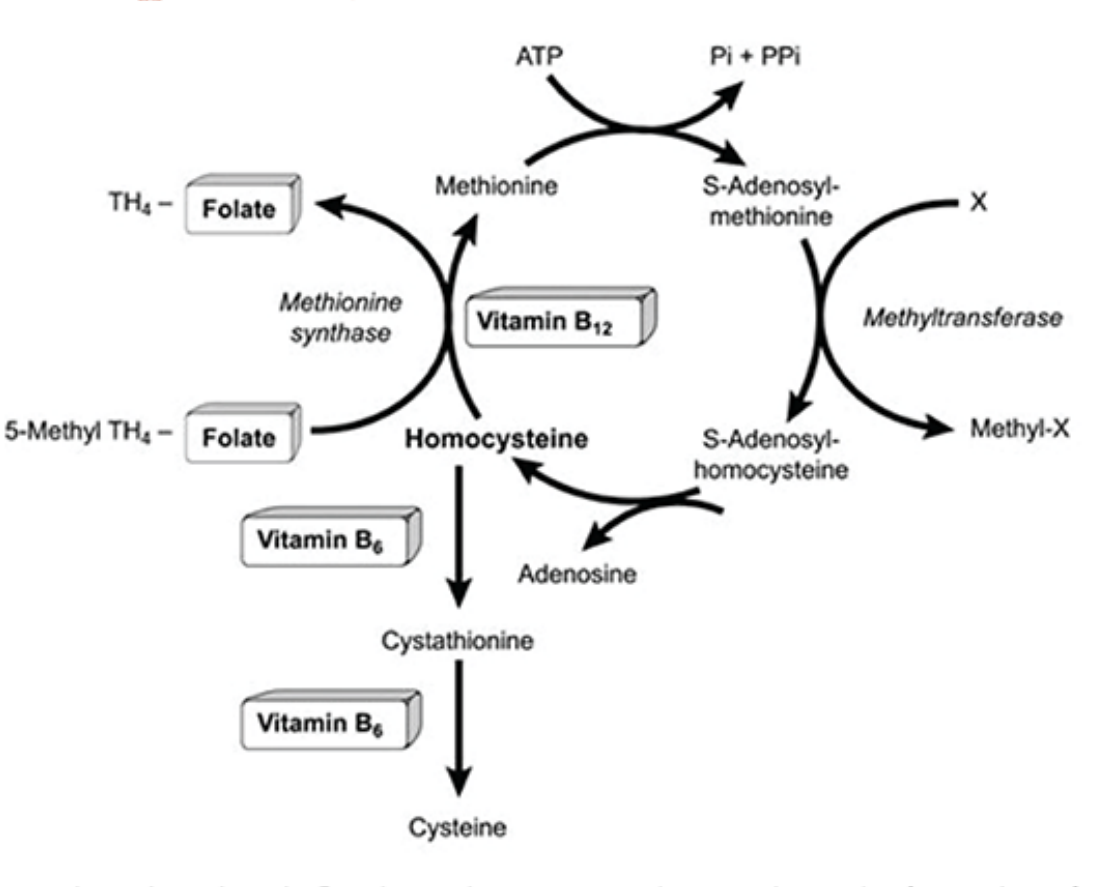
Vitamin B_{12} has the largest and most complex chemical structure of all the vitamins. It is unique among vitamins in that it contains a metal ion, cobalt. For this reason cobalamin is the term used to refer to compounds having vitamin B_{12} activity. Methylcobalamin and 5-deoxyadenosylcobalamin are the forms of vitamin B_{12} used in the human body (1). The form of cobalamin used in most nutritional supplements and fortified foods, cyanocobalamin, is readily converted to 5-deoxyadenosylcobalamin and methylcobalamin in the body. In mammals, cobalamin is a cofactor for only two enzymes, methionine synthase and L-methylmalonyl-coenzyme A mutase (2).

Function

Cofactor for methionine synthase

Methylcobalamin is required for the function of the folate-dependent enzyme, methionine synthase. This enzyme is required for the synthesis of the amino acid, methionine, from homocysteine. Methionine in turn is required for the synthesis of S-adenosylmethionine, a methyl group donor used in many biological methylation reactions, including the methylation of a number of sites within DNA, RNA, and proteins (3). Aberrant methylation of DNA and proteins, which causes alterations in chromatin structure and gene expression, are a common feature of cancer cells. Inadequate function of methionine synthase can lead to an accumulation of homocysteine, which has been associated with increased risk of cardiovascular disease (**Figure 1**).

Figure 1. Vitamin B_{12} and Homocysteine Metabolism

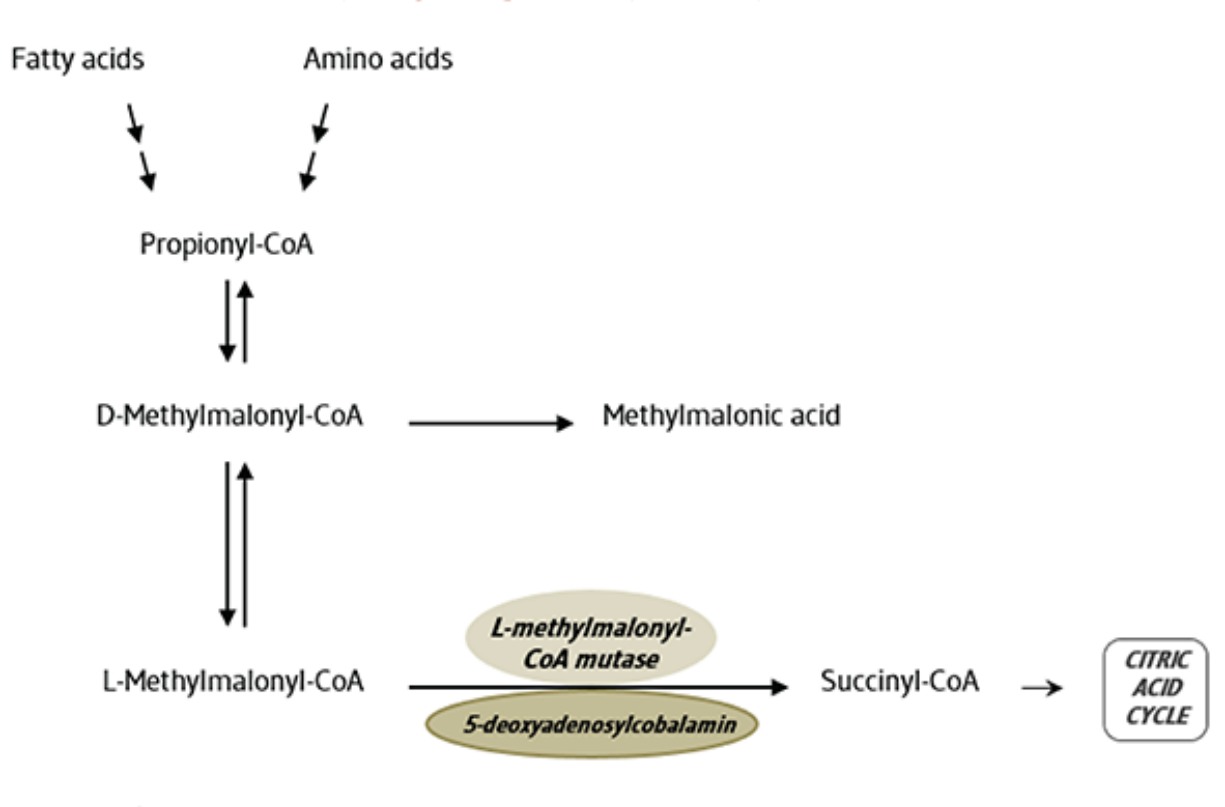


Methionine synthase is a vitamin B_{12}-dependent enzyme that catalyzes the formation of methionine from homocysteine using 5-methyltetrahydrofolate (5-methyl TH_4), a folate derivative, as a methyl donor. Another pathway catalyzed by betaine homocysteine methyltransferase also remethylates homocysteine to methionine using betaine as a methyl donor (not shown here). Methionine, in the form of S-adenosylmethionine, is required for most biological methylation reactions, including DNA methylation.

Cofactor for L-methylmalonyl-coenzyme A mutase

5-Deoxyadenosylcobalamin is required by the enzyme that catalyzes the conversion of L-methylmalonyl-coenzyme A to succinyl-coenzyme A (succinyl-CoA), which then enters the citric acid cycle (**Figure 2**). Succinyl-CoA plays an important role in the production of energy from lipids and proteins and is also required for the synthesis of hemoglobin, the oxygen-carrying pigment in red blood cells (3).

Figure 2. Metabolic Pathway Requiring 5-deoxyadenosylcobalamin



CoA, coenzyme A.

Deficiency

In healthy adults, vitamin B_{12} deficiency is uncommon, mainly because total body stores can exceed 2,500 µg, daily turnover is slow, and dietary intake of only 2.4 µg/day is sufficient to maintain adequate vitamin B_{12} status (see RDA) (4). In elderly individuals, vitamin B_{12} deficiency is more common mainly because of impaired intestinal absorption that can result in marginal to severe vitamin B_{12} deficiency in this population.

Causes of vitamin B_{12} deficiency

Intestinal malabsorption, rather than inadequate dietary intake, can explain most cases of vitamin B_{12} deficiency (5). Absorption of vitamin B_{12} from food requires normal function of the stomach, pancreas, and small intestine. Stomach acid and enzymes free vitamin B_{12} from food, allowing it to bind to R-protein (also known as transcobalamin-1 or haptocorrin), found in saliva and gastric fluids. In the alkaline environment of the small intestine, R-proteins are degraded by pancreatic enzymes, freeing vitamin B_{12} to bind to intrinsic factor (IF), a protein secreted by specialized cells in the stomach. Receptors on the surface of the ileum (final part of the small intestine) take up the IF-B_{12} complex only in the presence of calcium, which is supplied by the pancreas (5). Vitamin B_{12} can also be absorbed by passive diffusion, but this process is very inefficient—only about 1% absorption of the vitamin B_{12} dose is absorbed passively (2). The prevalent causes of vitamin B_{12} deficiency are (1) an autoimmune condition known as pernicious anemia, and (2) a disorder called food-bound vitamin B_{12} malabsorption. Both conditions have been associated with a chronic inflammatory disease of the stomach known as atrophic gastritis.

Atrophic gastritis

Atrophic gastritis is thought to affect 10%-30% of people over 60 years of age (6). The condition is frequently associated with the presence of autoantibodies directed toward stomach cells (see Pernicious anemia) and/or infection by the bacteria, *Helicobacter pylori* (*H. pylori*) (7). *H. pylori* infection induces chronic inflammation of the stomach, which may progress to peptic ulcer disease, atrophic gastritis, and/or gastric cancer in some individuals. Diminished gastric function in individuals with atrophic gastritis can result in bacterial overgrowth in the small intestine and cause food-bound vitamin B_{12} malabsorption. Vitamin B_{12} levels in serum, plasma, and gastric fluids are significantly decreased in individuals with *H. pylori* infection, and eradication of the bacteria has been shown to significantly improve vitamin B_{12} serum concentrations (8).

Pernicious anemia

Pernicious anemia has been estimated to be present in approximately 2% of individuals over 60 years of age (9). Although anemia is often a symptom, the condition is actually the end stage of an autoimmune inflammation of the stomach known as autoimmune atrophic gastritis, resulting in destruction of stomach cells by one's own antibodies (autoantibodies). Progressive destruction of the cells that line the stomach causes decreased secretion of acid and enzymes required to release food-bound vitamin B_{12}. Antibodies to intrinsic factor (IF) bind to IF preventing formation of the IF-B_{12} complex, further inhibiting vitamin B_{12} absorption. About 20% of the relatives of pernicious anemia patients also have the condition, suggesting a genetic predisposition. It is also thought that *H. pylori* infection could be involved in initiating the autoimmune response in a subset of individuals (10). Further, co-occurrence of autoimmune atrophic gastritis with other autoimmune conditions, especially autoimmune thyroiditis and type 1 diabetes mellitus, has been reported (11, 12).

Treatment of pernicious anemia generally requires injections of vitamin B_{12} to bypass intestinal absorption. High-dose oral supplementation is another treatment option, because consuming 1,000 µg (1 mg)/day of vitamin B_{12} orally should result in the absorption of about 10 µg/day (1% of dose) by passive diffusion. In fact, high-dose oral therapy is considered to be as effective as intramuscular injection (4).

Food-bound vitamin B_{12} malabsorption

Food-bound vitamin B_{12} malabsorption is defined as an impaired ability to absorb food- or protein-bound vitamin B_{12}; individuals with this condition can fully absorb the free form (13). While the condition is the major cause of poor vitamin B_{12} status in the elderly population, it is usually associated with atrophic gastritis, a chronic inflammation of the lining of the stomach that ultimately results in the loss of glands in the stomach (atrophy) and decreased stomach acid production (see Atrophic gastritis). Because stomach acid is required for the release of vitamin B_{12} from the proteins in food, vitamin B_{12} absorption is diminished. Decreased stomach acid production also provides an environment conducive to the overgrowth of anaerobic bacteria in the stomach, which further interferes with vitamin B_{12} absorption (3). Because vitamin B_{12} in supplements is not bound to protein, and because intrinsic factor (IF) is still available, the absorption of supplemental vitamin B_{12} is not reduced as it is in pernicious anemia. Thus, individuals with food-bound vitamin B_{12} malabsorption do not have an increased requirement for vitamin B_{12}; they simply need it in the crystalline form found in fortified foods and dietary supplements.

Other causes of vitamin B_{12} deficiency

Other causes of vitamin B_{12} deficiency include surgical resection of the stomach or portions of the small intestine where receptors for the IF-B_{12} complex are located. Conditions affecting the small intestine, such as malabsorption syndromes (celiac disease and tropical sprue), may also result in vitamin B_{12} deficiency. Because the pancreas provides critical enzymes, as well as calcium required for vitamin B_{12} absorption, pancreatic insufficiency may contribute to vitamin B_{12} deficiency. Since vitamin B_{12} is found only in foods of animal origin, a strict vegetarian (vegan) diet has resulted in cases of vitamin B_{12} deficiency. Moreover, alcoholics may experience reduced intestinal absorption of vitamin B_{12} (2), and individuals with acquired immunodeficiency syndrome (AIDS) appear to be at increased risk of deficiency, possibly related to a failure of the IF-B_{12} receptor to take up the IF-B_{12} complex (3). Further, long-term use of acid-reducing drugs has also been implicated in vitamin B_{12} deficiency (see Drug interactions).

Inherited disorders of vitamin B_{12} absorption

Rare cases of inborn errors of vitamin B_{12} metabolism have been reported in the literature (reviewed in 5). Imerslund-Gräsbeck syndrome is an inherited vitamin B_{12} malabsorption syndrome that causes megaloblastic anemia and neurologic disorders of variable severity in affected subjects. Similar clinical symptoms are found in individuals with hereditary IF deficiency (also called congenital pernicious anemia) in whom the lack of IF results in the defective absorption of vitamin B_{12}. Additionally, mutations affecting vitamin B_{12} transport in the body have been identified (14).

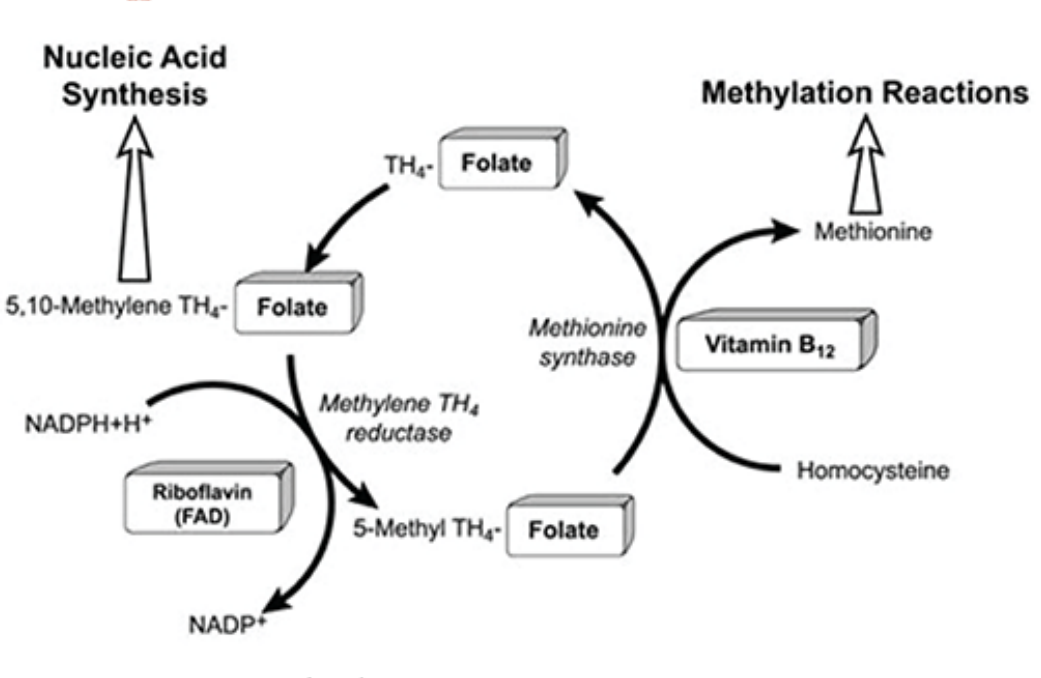
Symptoms of vitamin B_{12} deficiency

Vitamin B_{12} deficiency results in impairment of the activities of vitamin B_{12}-requiring enzymes. Impaired activity of methionine synthase results in elevated homocysteine levels, while impaired activity of L-methylmalonyl-CoA mutase results in increased levels of a metabolite of methylmalonyl-CoA called methylmalonic acid (MMA). While individuals with mild vitamin B_{12} deficiency may not experience symptoms, blood levels of homocysteine and/or MMA may be elevated (15).

Megaloblastic anemia

Diminished activity of methionine synthase in vitamin B_{12} deficiency inhibits the regeneration of tetrahydrofolate (THF) and traps folate in a form that is not usable by the body (**Figure 3**), resulting in symptoms of folate deficiency even in the presence of adequate folate levels. Thus, in both folate and vitamin B_{12} deficiencies, folate is unavailable to participate in DNA synthesis. This impairment of DNA synthesis affects the rapidly dividing cells of the bone marrow earlier than other cells, resulting in the production of large, immature, hemoglobin-poor red blood cells. The resulting anemia is known as megaloblastic anemia and is the symptom for which the disease, pernicious anemia, was named (3). Supplementation with folic acid will provide enough usable folate to restore normal red blood cell formation. However, if vitamin B_{12} deficiency is the cause, it will persist despite the resolution of the anemia. Thus, megaloblastic anemia should not be treated with folic acid until the underlying cause has been determined (16).

Figure 3. Vitamin B_{12} and Nucleic Acid Metabolism



5,10-Methylene tetrahydrofolate (TH_4) is required for the synthesis of nucleic acids, while 5-methyl TH_4 is required for the formation of methionine from homocysteine. Methionine, in the form of S-adenosylmethionine, is required for many biological methylation reactions, including DNA methylation. Methylene TH_4 reductase is a flavin-dependent enzyme required to catalyze the reduction of 5,10-methylene TH_4 to 5-methyl TH_4.

Neurologic symptoms

The neurologic symptoms of vitamin B_{12} deficiency include numbness and tingling of the hands and, more commonly, the feet; difficulty walking; memory loss; disorientation; and dementia with or without mood changes. Although the progression of neurologic complications is generally gradual, such symptoms may not be reversed with treatment of vitamin B_{12} deficiency, especially if they have been present for a long time. Neurologic complications are not always associated with megaloblastic anemia and are the only clinical symptom of vitamin B_{12} deficiency in about 25% of cases (17). Although vitamin B_{12} deficiency is known to damage the myelin sheath covering cranial, spinal, and peripheral nerves, the biochemical processes leading to neurological damage in vitamin B_{12} deficiency are not yet fully understood (18).

Gastrointestinal symptoms

Tongue soreness, appetite loss, and constipation have also been associated with vitamin B_{12} deficiency. The origins of these symptoms are unclear, but they may be related to the stomach inflammation underlying some cases of vitamin B_{12} deficiency and to the progressive destruction of the lining of the stomach (17).

The Recommended Dietary Allowance (RDA)

The RDA for vitamin B_{12} was revised by the Food and Nutrition Board (FNB) of the US Institute of Medicine in 1998 (**Table 1**). Because of the increased risk of food-bound vitamin B_{12} malabsorption in older adults, the FNB recommended that adults over 50 years of age get most of the RDA from fortified food or vitamin B_{12}-containing supplements (17).

Table 1. Recommended Dietary Allowance (RDA) for Vitamin B_{12}

Life Stage	Age	Males (µg/day)	Females (µg/day)
Infants	0-6 months	0.4 (AI)	0.4 (AI)
Infants	7-12 months	0.5 (AI)	0.5 (AI)
Children	1-3 years	0.9	0.9
Children	4-8 years	1.2	1.2
Children	9-13 years	1.8	1.8
Adolescents	14-18 years	2.4	2.4
Adults	19-50 years	2.4	2.4
Adults	51 years and older	2.4*	2.4*
Pregnancy	all ages	-	2.6
Breast-feeding	all ages	-	2.8
*Vitamin B_{12} intake should be from supplements or fortified foods due to the age-related increase in food-bound malabsorption.			

Disease Prevention

Cardiovascular disease

As mentioned above, chronic atrophic gastritis and infection by *H. pylori* can cause deficiency in vitamin B_{12} secondary to malabsorption disorders (see Causes of vitamin B_{12} deficiency). However, the occurrence of *H. pylori* infection and chronic atrophic gastritis did not modify the five-year incidence of cardiovascular accidents (stroke and heart attack) or mortality in a large cohort study of nearly 10,000 men and women over 50 years old (19). Yet, vitamin B_{12} status was not assessed in this study, despite the high prevalence of vitamin B_{12} deficiency in older individuals.

Homocysteine and cardiovascular disease

Epidemiological studies indicate that even moderately elevated levels of homocysteine in the blood raise the risk of cardiovascular disease (CVD) (20), though the mechanism by which homocysteine may increase the CVD risk remains the subject of a great deal of research (21). The amount of homocysteine in the blood is regulated by at least three vitamins: folate, vitamin B_6, and vitamin B_{12} (see **Figure 1** above). An early analysis of the results of 12 randomized controlled trials showed that folic acid supplementation (0.5-5 mg/day) had the greatest lowering effect on blood homocysteine levels (25% decrease); co-supplementation with folic acid and vitamin B_{12} (500 µg/day) provided an additional 7% reduction (32% decrease) in blood homocysteine concentrations (22). The results of a sequential supplementation trial in 53 men and women indicated that after folic acid supplementation, vitamin B_{12} became the major determinant of plasma homocysteine levels (23). It is thought that the elevation of homocysteine levels might be partly due to vitamin B_{12} deficiency in individuals over 60 years of age. Two studies found blood methylmalonic acid (MMA) levels to be elevated in more than 60% of elderly individuals with elevated homocysteine levels. In the absence of impaired kidney function, an elevated MMA level in conjunction with elevated homocysteine suggests either a vitamin B_{12} deficiency or a combined vitamin B_{12} and folate deficiency (24). Thus, it appears important to evaluate vitamin B_{12} status, as well as kidney function, in older individuals with elevated homocysteine levels prior to initiating homocysteine-lowering therapy. For more information regarding homocysteine and CVD, see the article on Folate.

Intervention studies

Although increased intake of folic acid and vitamin B_{12} is effective in decreasing homocysteine levels, the combined intervention of these B vitamins did not lower risk for CVD. Indeed, several randomized, placebo-controlled trials have been conducted to determine whether homocysteine-lowering through folic acid, vitamin B_{12}, and vitamin B_6 supplementation reduces the incidence of CVD. A recent meta-analysis of data from 11 trials, including nearly 45,000 participants at risk of CVD, showed that B-vitamin supplementation had no significant effect on risk of myocardial infarction (heart attack) or stroke, nor did it modify the risk of all-cause mortality (25). Other meta-analyses that included patients with chronic kidney disease have confirmed the lack of effect of homocysteine-lowering on risk of myocardial infarction and death. However, stroke risk was significantly reduced by 7%-12% with the B-vitamin supplementation (26, 27). Another meta-analysis of 12 clinical trials measuring flow-mediated vasodilation (FMD; a surrogate marker of vascular health) in response to homocysteine reduction revealed that B-vitamin supplementation was accompanied by an improved FMD in short-term <8 weeks) but not in long-term studies conducted in subjects with preexisting vascular diseases (28). Yet, some of the studies included in these meta-analyses did not use vitamin B_{12}, and folate administration on its own has shown a protective role on vascular function and stroke risk (29). Besides, the high prevalence of malabsorption disorders and vitamin B_{12} deficiency in elderly individuals might warrant the use of higher doses of vitamin B_{12} than those used in these trials (30); in cases of malabsorption, only high-dose oral therapy or intramuscular injections can overcome vitamin B_{12} deficiency (4).

Cancer

Folate is required for synthesis of DNA, and there is evidence that decreased availability of folate results in strands of DNA that are more susceptible to damage. Deficiency of vitamin B_{12} traps folate in a form that is unusable by the body for DNA synthesis. Both vitamin B_{12} and folate deficiencies result in a diminished capacity for methylation reactions (see **Figure 3** above). Thus, vitamin B_{12} deficiency may lead to an elevated rate of DNA damage and altered methylation of DNA, both of which are important risk factors for cancer. A series of studies in young adults and older men indicated that increased levels of homocysteine and decreased levels of vitamin B_{12} in the blood were associated with a biomarker of chromosome breakage in white blood cells (reviewed in 31). In a double-blind, placebo-controlled study, the same biomarker of chromosome breakage was minimized in young adults who were supplemented with 700 µg of folic acid and 7 µg of vitamin B_{12} daily in cereal for two months (32).

Breast cancer

A case-control study compared prediagnostic levels of serum folate, vitamin B_6, and vitamin B_{12} in 195 women later diagnosed with breast cancer and 195 age-matched, cancer-free women. Among postmenopausal women, the association between blood levels of vitamin B_{12} and breast cancer suggested a threshold effect. The risk of breast cancer was more than doubled in women with serum vitamin B_{12} levels in the lowest quintile compared to women in the four highest quintiles (33). However, the meta-analysis of this study with three additional case-control studies found no protection associated with high compared to low vitamin B_{12} serum levels (34). A case-control study in Mexican women (475 cases and 1,391 controls) reported that breast cancer risk for women in the highest quartile of vitamin B_{12} intake (7.3-7.7 µg/day) was 68% lower than those in the lowest quartile (2.6 µg/day). Stratification of the data revealed that the inverse association between dietary vitamin B_{12} intake and breast cancer risk was stronger in postmenopausal women compared to premenopausal women, though both associations were statistically significant. Moreover, among postmenopausal women, the apparent protection conferred by folate was only observed in women with the highest vitamin B_{12} quartiles of intake (35). However, more recent case-control and prospective cohort studies have reported weak to no risk reduction with vitamin B_{12} intakes in different populations, including Hispanic, African American and European American women (36, 37). A meta-analysis of seven case-control and seven prospective cohort studies concluded that the risk of breast cancer was not modified by high versus low vitamin B_{12} intakes (34). There was no joint association between folate and vitamin B_{12} intakes and breast cancer risk. Presently, there is little evidence to suggest a relationship between vitamin B_{12} status and breast cancer. In addition, results from observational studies are not consistently in support of an association between high dietary folate intakes and reduced risk for breast cancer (see the article on Folate). There is a need to evaluate the effect of folate and vitamin B_{12} supplementation in well-controlled, randomized, clinical trials, while considering various factors that modify breast cancer risk, such as menopausal status, ethnicity, and alcohol intake.

Neural tube defects

Neural tube defects (NTD) may result in anencephaly or spina bifida, which are mostly fatal congenital malformations of the central nervous system. The defects arise from failure of embryonic neural tube to close, which occurs between the 21st and 28th days after conception, a time when many women are unaware of their pregnancy (38). Randomized controlled trials have demonstrated 60% to 100% reductions in NTD cases when women consumed folic acid supplements in addition to a varied diet during the month before and the month after conception. Increasing evidence indicates that the homocysteine-lowering effect of folic acid plays a critical role in reducing the risk of NTD (39). Homocysteine may accumulate in the blood when there is inadequate folate and/or vitamin B_{12} for effective functioning of the methionine synthase enzyme. Decreased vitamin B_{12} levels and elevated homocysteine concentrations have been found in the blood and amniotic fluid of pregnant women at high risk of NTD (40). The recent meta-analysis of 12 case-control studies, including 567 mothers with current or prior NTD-affected pregnancy and 1,566 unaffected mothers, showed that low maternal vitamin B_{12} status was associated with an increased risk of NTD (41). Yet, whether vitamin B_{12} supplementation may be beneficial in the prevention of NTD has not been evaluated (42).

Cognitive decline, dementia, and Alzheimer's disease

The occurrence of vitamin B_{12} deficiency prevails in the elderly population and has been frequently associated with Alzheimer's disease (reviewed in 43). One study found lower vitamin B_{12} levels in the cerebrospinal fluid of patients with Alzheimer's disease than in patients with other types of dementia, though blood levels of vitamin B_{12} did not differ (44). The reason for the association of low vitamin B_{12} status with Alzheimer's disease is not clear. Vitamin B_{12} deficiency, like folate deficiency, may lead to decreased synthesis of methionine and S-adenosylmethionine (SAM), thereby adversely affecting methylation reactions. Methylation reactions are essential for the metabolism of components of the myelin sheath of nerve cells as well as for synthesis of neurotransmitters (18). Other metabolic implications of vitamin B_{12} deficiency include the accumulation of homocysteine and methylmalonic acid, which might contribute to the neuropathologic features of dementia (43).

Observational studies

A large majority of cross-sectional and prospective cohort studies have associated elevated homocysteine concentrations with measures of poor cognitive scores and increased risk of dementia, including Alzheimer's disease (reviewed in 45). A case-control study of 164 patients with dementia of Alzheimer's type included 76 cases in which the diagnosis of Alzheimer's disease was confirmed by examination of brain cells after death. Compared to 108 control subjects without evidence of dementia, subjects with dementia of Alzheimer's type and confirmed Alzheimer's disease had higher blood homocysteine levels and lower blood levels of folate and vitamin B_{12}. Measures of general nutritional status indicated that the association of increased homocysteine levels and diminished vitamin B_{12} status with Alzheimer's disease was not due to dementia-related malnutrition (46). In a sample of 1,092 men and women without dementia followed for an average of 10 years, those with higher plasma homocysteine levels at baseline had a significantly higher risk of developing Alzheimer's disease and other types of dementia. Specifically, those with plasma homocysteine levels greater than 14 µmol/L had nearly double the risk of developing Alzheimer's disease (47). A study in 650 elderly men and women reported that the risk of elevated plasma homocysteine levels was significantly higher in those with lower cognitive function scores (48). A prospective study in 816 elderly men and women reported that those with hyperhomocysteinemia (homocysteine levels >15 µmol/L) had a significantly higher risk of developing Alzheimer's disease or dementia. Although raised homocysteine levels might be partly due to a poor vitamin B_{12} status, the latter was not related to risk of Alzheimer's disease or dementia in this study (49).

A recent systematic review of 35 prospective cohort studies assessing the association between vitamin B_{12} status and cognitive deterioration in older individuals with or without dementia at baseline did not support a relationship between vitamin B_{12} serum concentrations and cognitive decline, dementia, or Alzheimer's disease (50). Nevertheless, studies utilizing more sensitive biomarkers of vitamin B_{12} status, including measures of holo-transcobalamin (holo-TC; a vitamin B_{12} carrier) and methylmalonic acid, showed more consistent results and a trend toward associations between poor vitamin B_{12} status and faster cognitive decline and risk of Alzheimer's disease (51-55). Besides, it cannot be excluded that the co-occurrence of potential confounders like elevated homocysteine level and poor folate status might mitigate the true contribution of vitamin B_{12} status to cognitive functioning (45).

Intervention studies

High-dose B-vitamin supplementation has been proven effective for treating hyperhomocysteinemia in elderly individuals with or without cognitive impairment. However, homocysteine-lowering trials have produced equivocal results regarding the prevention of cognitive deterioration in this population. A systematic review and meta-analysis of 18 randomized, placebo-controlled trials examining the effect of B-vitamin supplementation did not find that the decrease in homocysteine level prevented or delayed cognitive decline among older subjects (56). A more recent randomized, double-blind, placebo-controlled clinical trial in 900 older individuals at high risk of cognitive impairment found that daily supplementation of 400 µg of folic acid and 100 µg of vitamin B_{12} for two years significantly improved measures of immediate and delayed memory and slowed the rise in plasma homocysteine concentrations (57). However, supplemented subjects had no reduction in homocysteine concentrations compared to baseline, nor did they perform better in processing speed tests compared to placebo. Another two-year, randomized, placebo-controlled study in elderly adults reported that a daily regimen of 800 µg of folic acid, 500 µg of vitamin B_{12}, and 20 mg of vitamin B_6 significantly reduced the rate of brain atrophy compared to placebo treatment (0.5% vs. 3.7%). Interestingly, a greater benefit was seen in those with high compared to low homocysteine concentrations at baseline, suggesting the importance of lowering homocysteine levels in prevention of brain atrophy and cognitive decline (58, 59). The authors attributed the changes in homocysteine levels primarily to vitamin B_{12} (59). Finally, the most recent randomized, double blind, placebo-controlled trial in over 2,500 individuals who suffered a stroke showed that the normalization of homocysteine concentrations by B-vitamin supplementation (2 mg of folic acid, 500 µg of vitamin B_{12}, and 25 mg of vitamin B_6) did not improve cognitive performance or decrease incidence of cognitive decline compared to placebo (60). Currently, there is a need for larger trials to evaluate the effect of B-vitamin supplementation on long-term outcomes, such as the incidence of Alzheimer's disease.

Depression

Observational studies have found as many as 30% of patients hospitalized for depression are deficient in vitamin B_{12} (61). A cross-sectional study of 700 community-living, physically disabled women over the age of 65 found that vitamin B_{12}-deficient women were twice as likely to be severely depressed as non-deficient women (62). A population-based study in 3,884 elderly men and women with depressive disorders found that those with vitamin B_{12} deficiency were almost 70% more likely to experience depression than those with normal vitamin B_{12} status (63). The reasons for the relationship between vitamin B_{12} deficiency and depression are not clear but may involve a shortage in S-adenosylmethionine (SAM). SAM is a methyl group donor for numerous methylation reactions in the brain, including those involved in the metabolism of neurotransmitters whose deficiency has been related to depression (64). Severe vitamin B_{12} deficiency in a mouse model showed dramatic alterations in the level of DNA methylation in the brain, which might lead to neurologic impairments (65). This hypothesis is supported by several studies that have shown supplementation with SAM improves depressive symptoms (66-69).

Increased homocysteine level is another nonspecific biomarker of vitamin B_{12} deficiency that has been linked to depressive symptoms in the elderly (70). However, in a recent cross-sectional study conducted in 1,677 older individuals, higher vitamin B_{12} plasma levels, but not changes in homocysteine concentrations, were correlated with a lower prevalence of depressive symptoms (71). Few studies have examined the relationship of vitamin B_{12} status, homocysteine levels, and the development of depression over time. In a randomized, placebo-controlled, intervention study with over 900 older participants experiencing psychological distress, daily supplementation with folic acid (400 µg) and vitamin B_{12} (100 µg) for two years did not reduce the occurrence of symptoms of depression despite significantly improving blood folate, vitamin B_{12}, and homocysteine levels compared to placebo (72). However, in a long-term randomized, double-blind, placebo-controlled study among sufferers of cerebrovascular accidents at high risk of depression, daily supplementation with 2 mg of folic acid, 25 mg of vitamin B_6, and 500 µg vitamin B_{12} significantly lowered the risk of major depressive episodes during a seven-year follow-up period compared to placebo (73). Although it cannot yet be determined whether vitamin B_{12} deficiency plays a causal role in depression, it may be beneficial to screen for vitamin B_{12} deficiency in older individuals as part of a medical evaluation for depression.

Osteoporosis

High homocysteine levels may affect bone remodeling by increasing bone resorption (breakdown), decreasing bone formation, and reducing bone blood flow. Another proposed mechanism involves the binding of homocysteine to the collagenous matrix of bone, which may modify collagen properties and reduce bone strength (reviewed in 74). Alterations of bone biomechanical properties can contribute to osteoporosis and increase the risk of fractures in the elderly. Since vitamin B_{12} is a determinant of homocysteine metabolism, it was suggested that the risk of osteoporotic fractures in older subjects might be enhanced by vitamin B_{12} deficiency. A meta-analysis of four observational studies, following a total of 7,475 older individuals for 3 to 16 years, found a weak association between an elevation in vitamin B_{12} of 50 picomoles/L in blood and a reduction in fracture risk (75). A randomized, placebo-controlled trial in 559 elderly individuals with low serum levels of folate and vitamin B_{12} and at increased risk of fracture evaluated the combined supplementation of very high doses of folic acid (5 mg/day) and vitamin B_{12} (1.5 mg/day). The two-year study found that the supplementation improved B-vitamin status, decreased homocysteine concentrations, and reduced risk of total fractures compared to placebo (76). However, a multicenter study in 5,485 subjects with cardiovascular disease or diabetes mellitus showed that daily supplementation with folic acid (2.5 mg), vitamin B_{12} (1 mg), and vitamin B_6 (50 mg) lowered homocysteine concentrations but had no effect on fracture risk compared to placebo (77). Another small, randomized, double blind trial in 93 individuals with low vitamin D status found no additional benefit of B-vitamin supplementation (50 mg/day of vitamin B_6, 0.5 mg/day of folic acid, and 0.5 mg/day of vitamin B_{12}) on markers of bone health over a one-year period beyond that associated with vitamin D and calcium supplementation. Yet, the short length of the study did not permit a conclusion on whether the lowering of homocysteine through B-vitamin supplementation could have long-term benefits on bone strength and fracture risk (78). A large intervention study conducted in older people with no preexisting conditions is under way to evaluate the effect of B-vitamin supplementation on markers of bone health and incidence of fracture; this trial might clarify whether B vitamins could have a protective effect on bone health in the elderly population (79).

Sources

Food sources

Only bacteria can synthesize vitamin B_{12} (80). Vitamin B_{12} is present in animal products, such as meat, poultry, fish (including shellfish), and to a lesser extent dairy products and eggs (1). Fresh pasteurized milk contains 0.9 µg per cup and is an important source of vitamin B_{12} for some vegetarians (17). Those strict vegetarians who eat no animal products (vegans) need supplemental vitamin B_{12} to meet their requirements. A few plant-source foods, such as certain fermented beans and vegetables and edible algae and mushrooms, may contain bioactive vitamin B_{12} (81). Together with B-vitamin fortified food and supplements, these foods might contribute, though modestly, to prevent vitamin B_{12} deficiency in individuals consuming vegetarian diets. Also, individuals over the age of 50 should obtain their vitamin B_{12} in supplements or fortified foods (e.g., fortified cereals) because of the increased likelihood of food-bound vitamin B_{12} malabsorption with increasing age.

Most people do not have a problem obtaining the RDA of 2.4 µg/day of vitamin B_{12} in food. According to a US national survey, the average dietary intake of vitamin B_{12} is 5.4 µg/day for adult men and 3.4 µg/day for adult women. Adults over the age of 60 had an average dietary intake of 4.8 µg/day (42). However, consumption of any type of vegetarian diet dramatically increases the prevalence of vitamin B_{12} deficiency in individuals across all age groups (82). Some foods with substantial amounts of vitamin B_{12} are listed in **Table 2**, along with their vitamin B_{12} content in micrograms (µg). For more information on the nutrient content of specific foods, search USDA's FoodData Central.

Table 2. Some Food Sources of Vitamin B_{12}

Food	Serving	Vitamin B_{12} (µg)
Clams (steamed)	3 ounces	84.1
Mussels (steamed)	3 ounces	20.4
Mackerel (Atlantic, cooked, dry-heat)	3 ounces*	16.1
Crab (Alaska king, steamed)	3 ounces	9.8
Beef (lean, plate steak, cooked, grilled)	3 ounces	6.9
Salmon (chinook, cooked, dry-heat)	3 ounces	2.4
Rockfish (cooked, dry-heat)	3 ounces	1.0
Milk (skim)	8 ounces	0.9
Turkey (cooked, roasted)	3 ounces	0.8
Brie (cheese)	1 ounce	0.5
Egg (poached)	1 large	0.4
Chicken (light meat, cooked, roasted)	3 ounces	0.3
*A three-ounce serving of meat or fish is about the size of a deck of cards.		

Supplements

Cyanocobalamin is the principal form of vitamin B_{12} used in oral supplements, but methylcobalamin is also available as a supplement. Cyanocobalamin is available by prescription in an injectable form and as a nasal gel for the treatment of pernicious anemia. Over-the-counter preparations containing cyanocobalamin include multivitamins, vitamin B-complex supplements, and single-nutrient, vitamin B_{12} supplements (83).

Safety

Toxicity

No toxic or adverse effects have been associated with large intakes of vitamin B_{12} from food or supplements in healthy people. Doses as high as 2 mg (2,000 µg) daily by mouth or 1 mg monthly by intramuscular (IM) injection have been used to treat pernicious anemia without significant side effects (84). When high doses of vitamin B_{12} are given orally, only a small percentage can be absorbed, which may explain the low toxicity (4). Because of the low toxicity of vitamin B_{12}, no tolerable upper intake level (UL) has been set by the US Food and Nutrition Board (17).

Drug interactions

A number of drugs reduce the absorption of vitamin B_{12}. Proton-pump inhibitors (e.g., omeprazole and lansoprazole), used for therapy of Zollinger-Ellison syndrome and gastroesophageal reflux disease (GERD), markedly decrease stomach acid secretion required for the release of vitamin B_{12} from food but not from supplements. Long-term use of proton-pump inhibitors has been found to decrease blood vitamin B_{12} levels. However, vitamin B_{12} deficiency does not generally develop until after at least three years of continuous therapy (85, 86). Another class of gastric acid inhibitors known as histamine$_2$ (H_2)-receptor antagonists (e.g., cimetidine, famotidine, and ranitidine), often used to treat peptic ulcer disease, has also been found to decrease the absorption of vitamin B_{12} from food. It is not clear whether the long-term use of H_2-receptor antagonists could cause overt vitamin B_{12} deficiency (87, 88). Individuals taking drugs that inhibit gastric acid secretion should consider taking vitamin B_{12} in the form of a supplement because gastric acid is not required for its absorption. Other drugs found to inhibit vitamin B_{12} absorption from food include cholestyramine (a bile acid-binding resin used in the treatment of high cholesterol), chloramphenicol and neomycin (antibiotics), and colchicine (medicine for gout treatment). Metformin, a medication for individuals with type 2 diabetes, was found to decrease vitamin B_{12} absorption by tying up free calcium required for absorption of the IF-B_{12} complex (89). However, the clinical significance of this is unclear (90). It is not known whether calcium supplementation can reverse vitamin B_{12} malabsorption; therefore, calcium supplementation is not currently prescribed for the prevention or treatment of metformin-induced vitamin B_{12} deficiency (91). Previous reports that megadoses of vitamin C destroy vitamin B_{12} have not been supported (92) and may have been an artifact of the assay used to measure vitamin B_{12} levels (17).

Nitrous oxide, a commonly used anesthetic, oxidizes and inactivates vitamin B_{12}, thus inhibiting both of the vitamin B_{12}-dependent enzymes, and can produce many of the clinical features of vitamin B_{12} deficiency, such as megaloblastic anemia or neuropathy. Since nitrous oxide is commonly used for surgery in the elderly, some experts feel vitamin B_{12} deficiency should be ruled out prior to its use (6, 15).

Large doses of folic acid given to an individual with an undiagnosed vitamin B_{12} deficiency could correct megaloblastic anemia without correcting the underlying vitamin B_{12} deficiency, leaving the individual at risk of developing irreversible neurologic damage (17). For this reason, the Food and Nutrition Board of the US Institute of Medicine advises that all adults limit their intake of folic acid (supplements and fortification) to 1,000 µg (1 mg) daily.

Linus Pauling Institute Recommendation

A varied diet should provide enough vitamin B_{12} to prevent deficiency in most individuals 50 years of age and younger. Strict vegetarians and women planning to become pregnant should take a multivitamin supplement daily or eat fortified cereal, which would ensure a daily intake of 6 to 30 µg of vitamin B_{12} in a form that is easily absorbed. Higher doses of vitamin B_{12} supplements are recommended for patients taking medications that interfere with its absorption (see Drug interactions).

Older adults (>50 years)

Because vitamin B_{12} malabsorption and vitamin B_{12} deficiency are more common in older adults, the Linus Pauling Institute recommends that adults older than 50 years take 100 to 400 µg/day of supplemental vitamin B_{12}.

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Vitamin C

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Español

Summary

- Vitamin C, also known as L-ascorbic acid, is a water-soluble vitamin. Unlike most mammals and other animals, humans do not have the ability to synthesize vitamin C and must obtain it from the diet. *(More information)*
- Vitamin C is an essential cofactor in numerous enzymatic reactions, e.g., in the biosynthesis of collagen, carnitine, and neuropeptides, and in the regulation of gene expression. It is also a potent antioxidant. *(More information)*
- Prospective cohort studies indicate that higher vitamin C status, assessed by measuring circulating vitamin C, is associated with lower risks of hypertension, coronary heart disease, and stroke. *(More information)*
- There is some evidence to suggest that vitamin C may be a useful adjunct to conventional medical practice to reduce myocardial injury and arrhythmia following a cardiac procedure or surgery in patients with cardiovascular disease. *(More information)*
- There are insufficient data to suggest a link between vitamin C status and the risk of developing a given type of cancer. Most observational studies examining vitamin C intake in relation to cancer incidence have found no association. Randomized controlled trials have reported no effect of vitamin C supplementation on cancer risk. *(More information)*
- Current evidence of the efficacy of intravenous vitamin C in cancer patients is limited to observational studies, uncontrolled interventions, and case reports. There is a need for large, longer-duration phase II clinical trials that test the efficacy of intravenous vitamin C in cancer progression and overall survival. *(More information)*
- Overall, regular use of vitamin C supplements shortens the duration of the common cold but does not reduce the risk of becoming ill. Taking supplements once cold symptoms have already begun has no proven benefits. *(More information)*
- Vitamin C supplements are available in many forms, but there is little scientific evidence that any one form is better absorbed or more effective than another. *(More information)*
- There is no scientific evidence that large amounts of vitamin C (up to 10 grams [g]/day in adults) exert any adverse or toxic effects. An upper intake level of 2 g/day is recommended in order to prevent some adults from experiencing diarrhea and gastrointestinal disturbances. *(More information)*
- Supplemental vitamin C increases urinary oxalate concentrations, but whether an increase in urinary oxalate elevates the risk for kidney stones is not yet known. Those predisposed for kidney stone formation may consider avoiding high-dose (≥1 g/day) vitamin C supplementation. *(More information)*

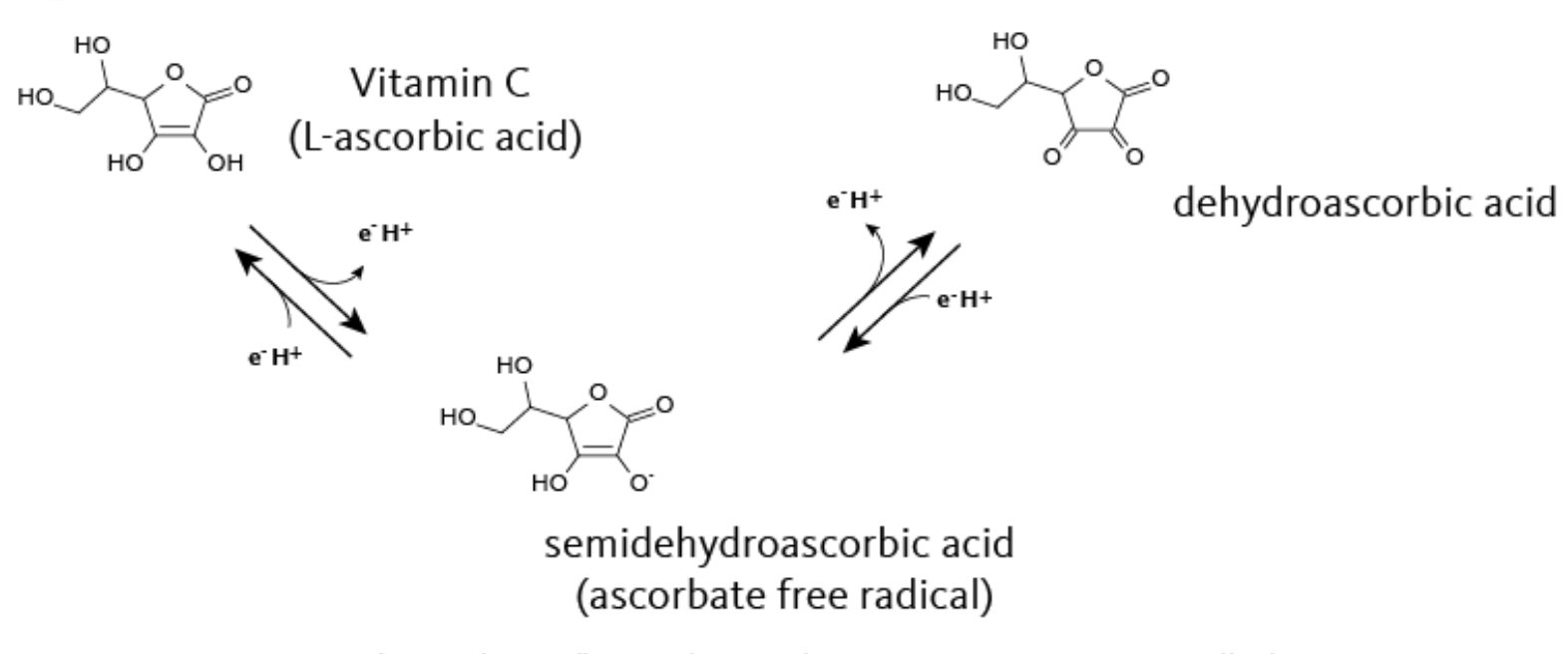
Function

Vitamin C (L-ascorbic acid) is a potent reducing agent, meaning that it readily donates electrons to recipient molecules (**Figure 1**). Related to this oxidation-reduction (redox) potential, two major functions of vitamin C are as an antioxidant and as an enzyme cofactor (1).

Vitamin C is the primary water-soluble, non-enzymatic antioxidant in plasma and tissues. Even in small amounts, vitamin C can protect indispensable molecules in the body, such as proteins, lipids (fats), carbohydrates, and nucleic acids (DNA and RNA), from damage by free radicals and reactive oxygen species (ROS) that are generated during normal metabolism, by active immune cells, and through exposure to toxins and pollutants (e.g., certain chemotherapy drugs and cigarette smoke). Vitamin C also participates in redox recycling of other important antioxidants; for example, vitamin C is known to regenerate vitamin E from its oxidized form (see the article on Vitamin E).

The role of vitamin C as a cofactor is also related to its redox potential. By maintaining enzyme-bound metals in their reduced forms, vitamin C assists mixed-function oxidases in the synthesis of several critical biomolecules (1). These enzymes are either monooxygenases or dioxygenases (see **Table 1**). Symptoms of vitamin C deficiency, such as poor wound healing and lethargy, likely result from the impairment of these vitamin C-dependent enzymatic reactions leading to the insufficient synthesis of collagen, carnitine, and catecholamines (see Deficiency). Moreover, several dioxygenases involved in the regulation of gene expression and the maintenance of genome integrity require vitamin C as a cofactor. Indeed, research has recently uncovered the crucial role played by enzymes, such as the TET dioxygenases and Jumonji domain-containing histone demethylases, in the fate of cells and tissues (see **Table 1**). These enzymes contribute to the epigenetic regulation of gene expression by catalyzing reactions involved in the demethylation of DNA and histones.

Figure 1. Vitamin C



Vitamin C (L-ascorbic acid) is an electron donor. Vitamin C can sequentially donate two electrons. Vitamin C can donate electrons to reactive free radicals, which then become reduced. The loss of one electron results in vitamin C being oxidized to the ascorbate free radical, which is relatively unreactive compared to other free radicals. The ascorbate free radical can be reduced to vitamin C by gaining one electron or be further oxidized to dehydroascorbic acid by losing another electron. Dehydroascorbic acid is only stable for a few minutes and is then either irreversibly hydrolyzed to form 2,3-diketogulonic acid or reduced to semidehydroascorbic acid and vitamin C (not shown here). However, the efficacy of the *in vivo* reduction reactions that yield vitamin C from dehydroascorbic acid and semidehydroascorbic acid appears to be low as vitamin C deficiency occurs in 30 days when vitamin C is removed from the diet of healthy people. Thus, most of the vitamin C is likely oxidized to dehydroascorbic acid, which is irreversibly metabolized.

[Figure 1 - Click to Enlarge]

Table 1. Enzymes Requiring Vitamin C as a Cofactor in Mammals (1, 2)

Enzymes*	Functions
Monooxygenases	
Dopamine β-monooxygenase	Norepinephrine (Noradrenaline) biosynthesis
Peptidyl-glycine α-amidating monooxygenase	Amidation of peptide hormones
Dioxygenases	
3 Prolyl 4-hydroxylase isoenzymes	Collagen hydroxylation
3 Prolyl 3-hydroxylase isoenzymes	Collagen hydroxylation
3 Lysyl hydroxylase isoenzymes	Collagen hydroxylation
4 Hypoxia-inducible factor (HIF) isoenzymes	HIF hydroxylation
Trimethyllysine hydroxylase	Carnitine biosynthesis
γ-Butyrobetaine hydroxylase	Carnitine biosynthesis
4-Hydroxyphenylpyruvate dioxygenase	Tyrosine metabolism
Ten-eleven translocation (TET) family of dioxygenases	Demethylation of DNA
Jumonji domain-containing histone demethylases	Demethylation of histones
*Monooxygenases catalyze the hydroxylation of one substrate, whereas dioxygenases catalyze a reaction that couples the hydroxylation of a specific substrate with the conversion (decarboxylation) of α-ketoglutarate into succinate.	

The capacity of vitamin C to influence the methylation status of DNA and histones in mammalian cells supports a role for the vitamin in health and disease beyond what was previously understood, in particular by safeguarding genome integrity (3, 4).

Role in immunity

Vitamin C affects several components of the human immune system *in vitro*; for example, vitamin C has been shown to stimulate both the production (5-9) and function (10, 11) of leukocytes (white blood cells), especially neutrophils, lymphocytes, and phagocytes. Specific measures of functions stimulated by vitamin C include cellular motility (10), chemotaxis (10, 11), and phagocytosis (11). Neutrophils, mononuclear phagocytes, and lymphocytes accumulate vitamin C to high concentrations, which can protect these cell types from oxidative damage (12-14). In response to invading microorganisms, phagocytic leukocytes release non-specific toxins, such as superoxide radicals, hypochlorous acid ("bleach"), and peroxynitrite; these reactive oxygen species kill pathogens and, in the process, can damage the leukocytes themselves (15). Vitamin C, through its antioxidant functions, has been shown to protect leukocytes from self-inflicted oxidative damage (14). Phagocytic leukocytes also produce and release cytokines, including interferons, which have antiviral activity (16). Vitamin C has been shown to increase interferon production *in vitro* (17). Additional studies have reported that vitamin C enhances the chemotactic and microbial killing capacities of neutrophils and stimulates the proliferation and differentiation of B- and T-lymphocytes (reviewed in 18).

It is widely thought by the general public that vitamin C boosts immune function, yet human studies published to date are conflicting. Disparate results are likely due to study design issues, often linked to a lack of understanding of vitamin C pharmacokinetics and requirements (19, 20).

Finally, vitamin C increases the bioavailability of iron from foods by enhancing intestinal absorption of non-heme iron (see the article on Iron) (21).

Bioavailability

Depletion-repletion pharmacokinetic experiments demonstrated that plasma vitamin C concentration is tightly controlled by three primary mechanisms: intestinal absorption, tissue transport, and renal reabsorption (22). In response to increasing oral doses of vitamin C, plasma vitamin C concentration rises steeply at intakes between 30 and 100 mg/day. Plasma concentrations of ascorbate reach steady-state at concentrations between 60 and 80 micromoles/L (μmol/L). This is typically observed at doses between 200 to 400 mg/day in healthy young adults, with some degree of individual variation (23, 24).

One hundred percent absorption efficiency is observed when ingesting vitamin C at doses up to 200 mg at a time. Higher doses (>500 mg) result in fractionally less vitamin C being absorbed as the dose increases. Once plasma vitamin C concentrations reach saturation, additional vitamin C is largely excreted in the urine. Notably, intravenous administration of vitamin C bypasses absorptive control in the intestine such that very high concentrations of vitamin C can be achieved in the plasma; within a few hours, renal excretion restores vitamin C to baseline plasma concentrations (see Cancer Treatment) (25).

While plasma vitamin C concentration reflects recent dietary intake, leukocyte (white blood cell) vitamin C is thought to be an indicator of body stores. However, leukocyte vitamin C concentration does not accurately reflect vitamin C in several tissues and may specifically underestimate vitamin C uptake into skeletal muscle (26). Yet, plasma concentrations of vitamin C ≥50 μmol/L are sufficient to saturate muscle tissue vitamin C.

There is also some limited evidence suggesting that individuals who carry certain polymorphisms in genes involved in vitamin C transport and detoxification mechanisms may have lower plasma vitamin C concentrations even with high vitamin C intakes (see also Vascular complications of diabetes mellitus) (reviewed in 27).

Due to the pharmacokinetics and tight regulation of plasma vitamin C, supplementation with vitamin C will have variable effects in vitamin C-replete (plasma concentrations near saturation) versus sub-optimal (plasma concentrations <50 μmol/L), marginally deficient (plasma concentrations <23 μmol/L), or severely deficient (plasma concentrations <11 μmol/L) individuals (28). Scientific studies investigating vitamin C efficacy to prevent or treat disease need to assess baseline vitamin C status before embarking on an intervention or statistical analysis (22, 29-31).

For a more detailed discussion on the bioavailability of different forms of vitamin C, see the article, The Bioavailability of Different Forms of Vitamin C.

Deficiency

Severe vitamin C deficiency has been known for many centuries as the potentially fatal disease, scurvy. By the late 1700s, the British navy was aware that scurvy could be cured by eating oranges or lemons, even though vitamin C would not be isolated until the early 1930s. Symptoms of scurvy include subcutaneous bleeding, poor wound closure, and bruising easily, hair and tooth loss, and joint pain and swelling. Such symptoms appear to be related to the weakening of blood vessels, connective tissue, and bone, which all contain collagen. Early symptoms of scurvy like fatigue may result from diminished levels of carnitine, which is needed to derive energy from fat, or from decreased synthesis of the catecholamine norepinephrine (see Function). Scurvy is rare in developed countries because it can be prevented by as little as 10 mg of vitamin C daily (32). However, cases have occurred in children and the elderly on very restricted diets (33, 34).

The Recommended Dietary Allowance (RDA)

The recommended dietary allowance (RDA) for vitamin C is based on the amount of vitamin C intake necessary to maintain neutrophil vitamin C concentration with minimal urinary excretion of vitamin C and is proposed to provide sufficient antioxidant protection (**Table 2**) (35). The recommended intake for smokers is 35 mg/day higher than for nonsmokers, because smokers are under increased oxidative stress from the toxins in cigarette smoke and generally have lower blood concentrations of vitamin C (36).

Table 2. Recommended Dietary Allowance (RDA) for Vitamin C

Life Stage	Age	Males (mg/day)	Females (mg/day)
Infants	0-6 months	40 (AI)	40 (AI)
Infants	7-12 months	50 (AI)	50 (AI)
Children	1-3 years	15	15
Children	4-8 years	25	25
Children	9-13 years	45	45
Adolescents	14-18 years	75	65
Adults	19 years and older	90	75
Smokers	19 years and older	125	110
Pregnancy	18 years and younger	-	80
Pregnancy	19 years and older	-	85
Breast-feeding	18 years and younger	-	115
Breast-feeding	19 years and older	-	120

Disease Prevention

The amount of vitamin C required to help prevent chronic disease is higher than the amount required for prevention of scurvy. Information regarding vitamin C and the prevention of chronic disease is based on both observational prospective cohort studies and randomized controlled trials (29, 37). Prospective cohort studies can examine the incidence of a specific disease in relation to vitamin C intake or body status in a cohort of participants who are followed over time. In contrast, trials are intervention studies that can establish a causal relationship between an exposure and an outcome, e.g., by evaluating the effect of vitamin C supplementation on the incidence of chronic disease in participants randomly assigned to receive either vitamin C or placebo for a given length of time.

Cardiovascular disease

Endothelial dysfunction

Endothelial dysfunction is considered to be an early step in the development of atherosclerosis. Alterations in the structure and function of the vascular endothelium that lines the inner surface of all blood vessels are associated with the loss of normal nitric oxide-mediated endothelium-dependent vasodilation. Endothelial dysfunction results in widespread vasoconstriction and coagulation abnormalities. The measurement of brachial artery flow-mediated dilation (FMD) is often used as a functional marker of endothelial function; FMD values are inversely correlated with the risk of future cardiovascular events (38). A 2014 meta-analysis of 44 randomized controlled trials in subjects with or without chronic diseases summarized the effect of supplemental vitamin C on endothelial function by measuring FMD (19 studies), assessing forearm blood flow (20 studies), or by pulse wave analysis (5 trials) (39). Short-term supplementation with vitamin C was found to reduce endothelial dysfunction in subjects with heart failure, atherosclerosis, or diabetes mellitus, but it had no effect in those with hypertension. Vitamin C also limited endothelial dysfunction that was experimentally induced in healthy volunteers (39). Improved endothelial function was observed with daily vitamin C doses above 500 mg (39).

Hypertension

Hypertension is a major risk factor for cardiovascular disease, including coronary heart disease, stroke, and atrial fibrillation. An analysis that combined data from three, large, independent prospective cohorts, (1) Nurses' Health Study 1 (NHS1; 88,540 women, median age 49 years); (2) Nurses' Health Study 2 (NHS2; 97,315 women, median age 36 years); and (3) Health Professionals Follow-up Study (HPFS; 37,375 men, median age 52 years), found no association between the level of vitamin C intake and risk of developing hypertension (40). On the other hand, when plasma vitamin C concentration was measured, cross-sectional studies have consistently indicated an inverse relationship between plasma vitamin C concentration and blood pressure in both men and women (41-43). A 15-year follow-up of about 2,500 participants in the Coronary Artery Risk Development in Young Adults (CARDIA) study found that higher plasma vitamin C and a higher diet quality score were independently associated with a reduced risk of developing hypertension (44). Interestingly, there was no relationship between diet score and risk of hypertension in those with the lowest plasma vitamin C, and plasma vitamin C was positively associated with risk of hypertension in those with low diet scores (44).

A meta-analysis of 29 small randomized controlled trials of short durations (median duration, 8 weeks) in 1,407 participants (10 to 120 subjects per trial; including both normotensive and hypertensive subjects) found that daily supplementation with 60 to 4,000 mg of vitamin C (median dose, 500 mg) reduced systolic blood pressure by 3.84 mm Hg and diastolic blood pressure by 1.48 mm Hg (45). Good quality long-term trials are needed to examine whether the anti-hypertensive effect of vitamin C is sustained over time and eventually results in a reduced risk of cardiovascular events.

It is important for individuals with significantly elevated blood pressure not to rely on vitamin C supplementation alone to reduce their hypertension. They should instead seek or continue treatment with anti-hypertensive medication and make dietary and lifestyle changes in consultation with their health care provider.

Cardiovascular disease risk

Coronary heart disease (CHD) is characterized by the buildup of plaque inside the arteries that supply blood to the heart (atherosclerosis). Over years of buildup and accumulated damage to the coronary arteries, CHD may culminate in a myocardial infarction or heart attack. Many prospective cohort studies have examined the relationship between vitamin C intake from diet and supplements and CHD risk, the results of which have been pooled and analyzed in two separate analyses (46, 47). In 2004, a pooled analysis of nine prospective cohort studies found that supplemental vitamin C intake (≥400 mg/day for a mean of 10 years), but not dietary vitamin C intake, was inversely associated with CHD risk (46). Conversely, a 2008 meta-analysis of 14 cohort studies concluded that dietary, but not supplemental, vitamin C intake was inversely related to CHD risk (47). The most recent large prospective cohort study found an inverse association between dietary vitamin C intake and CHD mortality in Japanese women, but not in men (48). In spite of the variable association depending on source, these analyses indicate an overall inverse association between higher vitamin C intakes and CHD risk.

Limitations inherent to dietary assessment methodology, such as recall bias, measurement error, and residual confounding, may account for some of the inconsistent associations between vitamin C intake and CHD risk. In order to overcome such limitations, some prospective studies measured plasma or serum concentrations of vitamin C as a more reliable index of vitamin C intake and biomarker of body vitamin C status.

The European Investigation into Cancer and Nutrition (EPIC)-Norfolk prospective cohort study investigated the relationship between vitamin C status and incident heart failure in healthy adults (9,187 men and 11,112 women, aged 58.1+/-9.2 years) (49). After a mean follow-up of 12.8 years, plasma vitamin C was inversely associated with incident cases of heart failure. Specifically, plasma vitamin C ranged from approximately 23 to 70 μmol/L in men and 33 to 82 μmol/L in women; across this range, every 20 μmol/L increase in plasma vitamin C was associated with a 9% reduction in risk of heart failure. Although a primary source of dietary vitamin C, consumption of fruit and vegetables — assessed by food frequency questionnaire — was not found to be associated with a lower risk of congestive heart failure (49). This highlights the fact that limitations associated with dietary assessment methods such as food frequency questionnaires may be overcome by using biomarkers of nutrient intake (50, 51).

A 2017 review of eight published randomized controlled trials found inconsistent results from seven trials reporting on the effect of vitamin C supplementation on serum cholesterol and triglycerides, established risk factors for cardiovascular disease (52). Only one large trial in more than 14,000 older men participating in the Physicians' Health Study II (PHS II) reported on cardiovascular outcomes. PHS II found that vitamin C supplementation (500 mg/day) for an average of eight years had no significant effect on major cardiovascular events, total myocardial infarction, or cardiovascular mortality (53). Notably, this study had several limitations (54), including no measurement of vitamin C status and the recruitment of a well-nourished study population.

There is a need for better quality studies to examine the effect of vitamin C on cardiovascular endpoints in participants with elevated risk of cardiovascular disease.

Stroke

A cerebrovascular event, or stroke, can be classified as hemorrhagic or ischemic. Hemorrhagic stroke occurs when a weakened blood vessel ruptures and bleeds into the surrounding brain tissue. Ischemic stroke occurs when an obstruction within a blood vessel blocks blood flow to the brain. Most (~80%) cerebrovascular events in high-income countries are ischemic in nature and associated with atherosclerosis as an underlying condition (55, 56).

With respect to vitamin C and cerebrovascular disease, a prospective cohort study that followed more than 2,000 residents of a rural Japanese community for 20 years found that the risk of stroke in those with the highest serum concentrations of vitamin C was 29% lower than in those with the lowest serum concentrations of vitamin C (57). Similarly, the EPIC-Norfolk study, a 10-year prospective cohort study in 20,649 adults, found that individuals with plasma vitamin C concentrations in the top quartile (25%) had a 42% lower risk of stroke compared to those in the lowest quartile (≥66 μmol/L vs. <41 μmol/L) (58). In both the Japanese (57) and EPIC-Norfolk (58) populations, blood vitamin C concentrations were highly correlated with fruit and vegetable intake. Therefore, as in many studies of vitamin C intake and chronic disease risk, it is difficult to separate the effects of vitamin C from the effects of other components of fruit and vegetables. For example, potassium — found at high levels in bananas, potatoes, and other fruit and vegetables — is known to be important in blood pressure regulation, and elevated blood pressure is a major risk factor for stroke (see the article on Potassium). A 2013 meta-analysis of 17 prospective cohort studies reported a 19% lower risk of stroke with the highest versus lowest dietary vitamin C intakes and a 38% lower risk with the highest versus lowest circulating vitamin C concentrations (59).

A randomized, double-blind, placebo-controlled trial in more than 14,000 older men participating in the Physicians' Health Study II (PHS II) found that vitamin C supplementation (500 mg/day) for an average of eight years had no significant effect on the incidence of or mortality from any type of stroke (53). Other trials also failed to show any evidence of an effect of vitamin C on the risk of stroke. A meta-analysis of 10 trials that examined antioxidant vitamins, of which five included vitamin C, found no association between any antioxidant vitamin (vitamin C, vitamin E, or β-carotene), administered alone or in combination, and risk of stroke (60).

Cancer

Overall, observational prospective cohort studies have reported no or modest inverse associations between vitamin C intake and the risk of developing a given type of cancer (37, 61-63). Additional detail is provided below for those cancer subtypes with substantial scientific information obtained from prospective cohort studies. Randomized, double-blind, placebo-controlled trials that have tested the effect of vitamin C supplementation (alone or in combination with other antioxidant nutrients) on cancer incidence or mortality have shown no effect (64).

Breast cancer

Two large prospective studies found dietary vitamin C intake to be inversely associated with breast cancer incidence in certain subgroups. In the Nurses' Health Study, premenopausal women with a family history of breast cancer who consumed an average of 205 mg/day of vitamin C from food had a 63% lower risk of breast cancer than those who consumed an average of 70 mg/day (65). In the Swedish Mammography Cohort, overweight women who consumed an average of 110 mg/day of vitamin C had a 39% lower risk of breast cancer compared to overweight women who consumed an average of 31 mg/day (66). More recent prospective cohort studies have reported no association between dietary and/or supplemental vitamin C intake and breast cancer (67-69).

Stomach cancer

A number of observational studies have found increased dietary vitamin C intake to be associated with decreased risk of gastric (stomach) cancer, and laboratory experiments indicate that vitamin C inhibits the formation of carcinogenic N-nitroso compounds in the stomach (70-72). A nested case-control study in the EPIC study found a 45% lower risk of gastric cancer incidence in individuals in the highest (≥51 μmol/L) versus lowest (<29 μmol/L) quartile of plasma vitamin C concentration; no association was observed between dietary vitamin C intake and gastric cancer (73).

Infection with the bacteria, *Helicobacter pylori* (*H. pylori*), is known to increase the risk of stomach cancer and is associated with lower vitamin C content of stomach secretions (74, 75). Although two intervention studies failed to show a reduction in stomach cancer incidence with vitamin C supplementation (35), some research suggests that vitamin C supplementation may be a useful addition to standard *H. pylori* eradication therapy in reducing the risk of gastric cancer (76). Because vitamin C can inactivate urease (an enzyme that facilitates *H. pylori* survival and colonization of the gastric mucosa at low pH) *in vitro*, vitamin C may be most effective as a prophylactic agent in those without achlorhydria (77, 78).

Colon cancer

By pooling data from 13 prospective cohort studies comprising 676,141 participants, it was determined that dietary intake of vitamin C was not associated with colon cancer, while total intake of vitamin C (i.e., from food and supplements) was associated with a 19% reduced risk of colon cancer (79). Each of the cohort studies used self-administered food frequency questionnaires at baseline to assess vitamin C intake. Although the analysis adjusted for several lifestyle and known risk factors, the authors noted that other healthy behaviors and/or folate intake may have confounded the association.

Non-Hodgkin lymphoma

A population-based, prospective study, the Iowa Women's Health Study, collected baseline data on diet and supplement use in 35,159 women (aged 55-69 years) and evaluated the risk of developing non-Hodgkin lymphoma (NHL) over 19 years of follow-up (80). Overall, an inverse association between fruit and vegetable intake and risk of NHL was observed. Additionally, dietary, but not supplemental, intake of vitamin C and other antioxidant nutrients (carotenoids, proanthocyanidins, and manganese) was inversely associated with NHL risk. Another large, multi-center, prospective study — the Women's Health Initiative — that followed 154,363 postmenopausal women for 11 years found that dietary and supplemental vitamin C intake at baseline was inversely associated with diffuse B-cell lymphoma, a subtype of NHL (81).

Other site-specific cancer types

The Physicians' Health Study II was a randomized, placebo-controlled trial that examined the effect of vitamin E (400 IU/day), vitamin C (500 mg/day), and a multivitamin supplement on the risk of cancer in 14,641 middle-aged male physicians over 10.3 years (7.6 years of active treatment plus 2.8 years post-treatment follow-up) (82). Supplementation with vitamin C had no effect on the overall risk of cancer or on the risk of prostate, bladder, or pancreatic cancer; there was a marginal reduction in colorectal cancer incidence with vitamin C compared to placebo (82).

Type 2 diabetes mellitus

In the National Institutes of Health (NIH)-American Association of Retired Persons (AARP) Diet and Health study that included 232,007 participants, the use of vitamin C supplements for at least seven times a week was associated with a 9% lower risk of developing type 2 diabetes mellitus compared to non-supplement use (83). In a cohort of 21,831 adults followed for 12 years in the EPIC-Norfolk study, high plasma vitamin C was found to be strongly associated with a reduced risk of diabetes (84). Additionally, several cross-sectional studies reported inverse associations between circulating vitamin C concentrations and markers of insulin resistance or glucose intolerance, such as glycated hemoglobin (HbA1c) concentration (50, 85, 86). Yet, short-term randomized controlled studies have found no effect of vitamin C supplementation on fasting glucose, fasting insulin, and HbA1c concentrations in healthy individuals (87). It is not known whether supplemental vitamin C could improve markers of glycemic control in subjects at risk of diabetes.

Adverse pregnancy outcomes

A 2015 meta-analysis of 29 randomized controlled trials found that administration of vitamin C during pregnancy, alone or in combination with a few other supplements, failed to reduce the risks of stillbirth, perinatal death, intrauterine growth restriction, preterm birth, premature rupture of membranes, and preeclampsia (88). Nonetheless, vitamin C supplementation led to a 36% lower risk of placental abruption and to a significant increase in gestational age at birth (88). Another meta-analysis of 40 randomized controlled trials in 276,820 women found no effect of vitamin C, alone or combined with vitamin E or multivitamins, when supplemented during pregnancy (starting prior to 20 weeks' gestation), on the risks of overall fetal loss, miscarriage, stillbirth, and congenital malformation (89).

Cigarette smoking during pregnancy causes intrauterine growth restriction and preterm birth, among other pregnancy complications (90, 91), and is the primary cause of childhood respiratory illness (92). For some still unclear reasons, smoking has been associated with a lower risk of preeclampsia during pregnancy (93). A secondary analysis of a multicenter, randomized, double-blind, placebo-controlled trial in nearly 10,000 pregnant women found no reduction in the risk of preeclampsia with supplemental vitamin C (1,000 mg/day) and vitamin E (400 IU/day), regardless of women's smoking status during pregnancy. However, antioxidant supplementation resulted in reduced risks of placental abruption and preterm birth in women who smoked during pregnancy but not in non-smokers (94). Another pilot multicenter trial found better lung function during the first week of life and lower risk of wheezing through one year of age in infants whose smoking mothers were randomized to receive vitamin C (500 mg/day) rather than a placebo during pregnancy (95). The Vitamin C to Decrease the Effects of Smoking in Pregnancy on Infant Lung Function [VCSIP] study is an ongoing trial designed to confirm these preliminary observations using more accurate measurements of pulmonary function in a larger sample of women randomized to receive supplemental vitamin C or placebo (96).

Alzheimer's disease

In the US, Alzheimer's disease (AD) is the most common form of dementia, affecting 5.5 million individuals 65 years and over (97). Oxidative stress, neuroinflammation, β-amyloid plaque deposition, Tau protein-forming tangles, and neuronal cell death in the brain of subjects affected by AD have been associated with cognitive decline and memory loss. Lower vitamin C concentrations in the cerebrospinal fluid (CSF) and brain extracellular matrix of a mouse model of AD were found to increase oxidative stress and accelerate amyloid deposition and disease progression (98). In another AD mouse model that was lacking the ability to synthesize vitamin C, supplementation with a high versus low dose of vitamin C reduced amyloid deposition in the cortex and hippocampus and limited blood-brain barrier impairments and mitochondrial dysfunction (99).

The majority of large, population-based studies examining the relationship of vitamin C intake or supplementation with AD incidence have reported null results (100). In contrast, observational studies reported lower plasma vitamin C concentrations in AD patients compared to cognitively healthy subjects (101) and found better cognitive function or lower risk of cognitive impairment with higher plasma vitamin C (100).

Few studies have measured vitamin C concentration in the CSF, which more closely reflects the vitamin C status of the brain. Vitamin C is concentrated in the brain through a combination of active transport into brain tissue and retention via the blood-brain barrier (100). Although CSF vitamin C is maintained at concentrations several-fold higher than plasma vitamin C, the precise function of vitamin C in cognitive function and AD etiology is not yet fully understood (102). In a small, longitudinal biomarker study in 32 individuals with probable AD, a higher CSF-to-plasma vitamin C ratio at baseline was associated with a slower rate of cognitive decline at one year of follow-up (103). Impaired blood-brain barrier integrity may affect the brain's ability to retain vitamin C and thus to maintain a high CSF-to-plasma vitamin C ratio. The significance of the CSF-to-plasma vitamin C ratio in AD progression requires further study.

The effect of vitamin C supplementation, in combination with other antioxidants, on CSF biomarkers and cognitive function has been examined in only a few trials involving AD patients. In a small (n=23), open-label trial, combined supplementation with vitamin C (1,000 mg/day) and vitamin E (400 IU/day) to AD patients taking a cholinesterase inhibitor significantly increased antioxidant levels and decreased lipoprotein oxidation in CSF after one year, but had no effect on the clinical course of AD compared to controls (104). A similar finding was obtained in a double-blind, randomized controlled trial in which combined supplementation with vitamin C (500 mg/day), vitamin E (800 IU/day), and α-lipoic acid (900 mg/day) for 16 weeks reduced lipoprotein oxidation in CSF but elicited no clinical benefit in individuals with mild-to-moderate AD (n=78) (105). In this latter trial, a greater decline in the Mini Mental State Examination (MMSE) score was observed in the supplemented group, however, the significance of this observation remains unclear. A third placebo-controlled trial in mildly cognitively impaired older adults (ages, 60-75 years) found that one-year supplementation with vitamin C (400 mg/day) and vitamin E (300 mg/day) improved antioxidant blood capacity but had no effect on MMSE scores (106).

At this time, avoidance of vitamin C deficiency or insufficiency, rather than supplementation in replete individuals, seems prudent for the promotion of healthy brain aging (101).

Cataracts

The lens of the eye focuses light, producing a clear, sharp image on the retina, a layer of tissue on the inside back wall of the eyeball. Age-related changes to the lens (thickening, loss of flexibility) and oxidative damage contribute to the formation of cataract, i.e., cloudiness or opacity in the lens that interferes with the clear focusing of images on the retina.

In humans, vitamin C concentration is about 15 to 20 times higher in the aqueous humor — fluid that fills the anterior and posterior chambers of the eye — than in plasma, suggesting that the vitamin may be playing an important role in the eye (107). Decreased vitamin C concentrations in the lens of the eye have been associated with increased severity of cataracts (108). A meta-analysis of observational studies found that a reduced risk of age-related cataract with higher dietary vitamin C intakes in case-control studies and with higher circulating vitamin C concentrations in cross-sectional studies. However, no such associations were found in pooled analyses of prospective cohort studies (109). In fact, two prospective cohort studies in Swedish men (110) and women (111) reported that high-dose single nutrient supplements of vitamin C were associated with an increased risk of cataract, especially in those on corticosteroid therapy.

A 2012 review of nine randomized controlled trials found no substantial effect of β-carotene, vitamin C, and vitamin E, administered individually or in combination over 2.1 to 12 years, on the risk of cataracts or cataract surgery (112). Although trials do not currently support the use of high-dose supplementation with vitamin C in cataract prevention, there is a consistent inverse association observed between high daily intake of fruit and/or vegetables (>5 servings/day) and risk of cataract (113).

Gout

Gout, a condition that afflicts more than 4% of US adults (114), is characterized by abnormally high blood concentrations of uric acid (urate) (115). Urate crystals may form in joints, resulting in inflammation and pain, as well as in the kidneys and urinary tract, resulting in kidney stones. The tendency to exhibit elevated blood uric acid concentrations and develop gout is often inherited; however, dietary and lifestyle modification may be helpful in both the prevention and treatment of gout (116). In an observational study that included 1,387 men, higher intakes of vitamin C were associated with lower serum concentrations of uric acid (117). In a cross-sectional study conducted in 4,576 African Americans, the odds of having hyperuricemia was associated with dietary intakes high in fructose, low in vitamin C, or with high fructose-to-vitamin C ratios (118). A prospective study that followed a cohort of 46,994 men for 20 years found that total daily vitamin C intake was inversely associated with incidence of gout, with higher intakes being associated with greater risk reductions (119). The results of this study also indicated that supplemental vitamin C may be helpful in the prevention of gout (119).

A 2011 meta-analysis of 13 randomized controlled trials in healthy individuals with elevated serum uric acid revealed that vitamin C supplementation (a median dose of 500 mg/day for a median duration of 30 days) modestly reduced serum uric acid concentrations by 0.35 mg/dL compared to placebo (120). Such a reduction falls within the range of assay variability and is unlikely to be clinically significant (121). An eight-week, open-label, controlled trial randomized 40 subjects with gout to receive either allopurinol (standard-of-care), vitamin C, or both treatments (122). The effect of vitamin C, alone or with allopurinol, decreasing serum uric acid was modest and much less than that of allopurinol alone. The trial did not examine the effect of vitamin C on other outcomes associated with gout (122).

Although observational studies suggested that supplemental vitamin C may be helpful to prevent incident and recurrent gout, this has not been demonstrated by intervention studies undertaken thus far. In addition, there is currently little evidence to support a role for vitamin C in the management of patients with gout (123).

Mortality

Two large prospective cohort studies assessed the relationship between dietary and supplemental vitamin C intakes and mortality. In the Vitamins and Lifestyle Study, 77,719 men and women (ages 50-76 years) were questioned at baseline on their use of dietary supplements during the previous 10 years (124). After five years of follow-up, vitamin C supplement use was associated with a small decreased risk of total mortality, although no association was found with cardiovascular disease- or cancer-specific mortality. In the second prospective cohort study, the Diet, Cancer and Health Study, 55,543 Danish adults (ages 50-64 years) were questioned at baseline about their lifestyle, diet, and supplement use during the previous 12 months (125). No association between dietary or supplemental intake of vitamin C and mortality was found after approximately 14 years of follow-up. In contrast, a 2014 meta-analysis of 10 prospective cohort studies in 17,696 women with breast cancer found a lower risk of total and breast cancer-specific mortality with higher supplemental and dietary vitamin C intakes (126). A 2012 meta-analysis of 29 trials found no effect of oral vitamin C, given alone or in combination with other antioxidants, on all-cause mortality (127).

In parallel to these dietary assessment studies, a strong inverse association between plasma vitamin C and mortality from all-causes, cardiovascular disease, and ischemic heart disease (and cancer in men only) was observed in the EPIC-Norfolk multicenter, prospective cohort study (128). After approximately four years of follow-up in 19,496 men and women (ages 45-79 years), a dose-response relationship was observed such that each 20 μmol/L increase in plasma vitamin C was associated with an estimated 20% risk reduction in all-cause mortality. Similarly, higher serum vitamin C concentrations were associated with decreased risks of cancer-specific and all-cause mortality in 16,008 adults from the US National Health and Nutrition Examination Survey (NHANES) III (1994-1998) (129).

Disease Treatment

Cardiovascular disease

Complications of cardiac procedures and surgeries

Periprocedural myocardial injury: Coronary angioplasty (also called percutaneous transluminal coronary angioplasty) is a nonsurgical procedure for treating obstructive coronary heart disease (CHD), including unstable angina pectoris, acute myocardial infarction, and multivessel CHD. Angioplasty involves temporarily inserting and inflating a tiny balloon into the clogged artery to help restore the blood flow to the heart. Periprocedural myocardial injury that occurs in up to one-third of patients undergoing otherwise uncomplicated angioplasty increases the risk of morbidity and mortality at follow-up.

One randomized, placebo-controlled trial has examined the effect of intravenous vitamin C administered to patients with stable angina undergoing elective coronary angioplasty (130). Administration of a 1-gram (g) vitamin C infusion one hour prior to the angioplasty reduced the concentrations of oxidative stress markers and improved microcirculatory perfusion compared to placebo (130). Another trial randomized 532 patients to receive a 3-g vitamin C infusion or a placebo (saline solution) within six hours prior to coronary angioplasty (131). Vitamin C treatment substantially reduced the incidence of periprocedural myocardial injury, as assessed by a reduction in the concentrations of two markers of myocardial injury, namely creatine kinase and troponin-I (131). A recent randomized controlled trial assessed the effect of vitamin C and vitamin E administration on reperfusion damage in patients who experienced acute myocardial infarction and underwent coronary angioplasty (see below) (132).

Myocardial reperfusion injury: Reperfusion injury refers to tissue damage occurring at the time of blood flow restoration (reperfusion) following transient ischemia. The heart muscle may become oxygen-deprived (ischemic) as the result of myocardial infarction or with aortic clamping during coronary artery bypass graft (CABG) surgery. Increased generation of reactive oxygen species (ROS) when the heart muscle's oxygen supply is restored might be an important contributor to myocardial damage occurring at reperfusion (133). Myocardial reperfusion injury leads to complications, such as reperfusion arrhythmias (see Atrial fibrillation) and myocardial stunning.

Vitamin C is depleted during and following cardiac surgery (134) and this might be due to the direct quenching of ROS, the regeneration of other antioxidants, and/or a massive synthesis of catecholamines (dopamine, epinephrine, norepinephrine) (135). Two randomized controlled trials conducted in the 1990s reported a reduction in reperfusion-induced oxidative stress and myocardial injury with intravenous (136) or oral (137) vitamin C administration prior to CABG surgery (reviewed in 135). A more recent randomized, double-blind, placebo-controlled trial has been designed to examine the effect of vitamin C and vitamin E administration on ischemia-reperfusion damage in 99 patients with acute myocardial infarction undergoing coronary angioplasty (132). Vitamin C infusion (sodium ascorbate: 3.20 mmol/min for 1 hour then 0.96 mmol/min for 2 hours) prior to reperfusion followed by oral supplementation with vitamin C (1 g/day) and vitamin E (400 IU/day) for 84 days effectively prevented a reduction in antioxidant capacity at reperfusion and for the next six to eight hours. The protocol also limited microvascular dysfunction (i.e., improved microcirculatory perfusion) and improved left ventricular ejection fraction at discharge (on day 84) (138, 139). However, no difference in the infarct size between antioxidant vitamin treatment and placebo was seen (138).

Atrial fibrillation: Atrial fibrillation is the most common type of cardiac arrhythmia. It is also a common post-cardiac surgery complication, leading to an increased risk of cardiovascular morbidity (e.g., heart failure, stroke) and mortality. Three meta-analyses of prospective cohort studies and randomized controlled trials have reported an overall reduction in the risk of post-operative atrial fibrillation following administration of primarily oral vitamin C (140-142). In most trials, participants received 2 g of vitamin C prior to undergoing CABG or valve replacement surgery and 1 to 2 g/day for five days post-surgery. Although only a minority of trials delivered vitamin C intravenously, this administration route appeared to be more effective at reducing the risk of atrial fibrillation — presumably due to higher plasma concentrations achieved (140). Of note, a subgroup analysis in one of the meta-analyses showed a reduction of post-operative atrial fibrillation with vitamin C in non US-based trials (10 trials) but no effect of vitamin C in US-based trials (5 trials) (140).

Cerebral ischemia-reperfusion injury

A small randomized controlled trial performed in 60 ischemic stroke patients showed that intravenous vitamin C administration (500 mg/day for 10 days, initiated day 1 post-stroke) had no effect on serum markers of oxidative stress or neurological outcomes compared to placebo (143).

Vascular complications of diabetes mellitus

Cardiovascular disease (CVD) is the leading cause of death in individuals with diabetes mellitus. The role of increased oxidative stress in the occurrence of vascular complications in subjects with diabetes has led to hypothesis that higher intakes of antioxidant nutrients could help lower the risk of CVD in diabetic subjects (144). A 2018 meta-analysis of randomized controlled trials investigating the effect of antioxidant vitamin supplementation in patients with type 2 diabetes found that most improvement in markers of oxidative stress and blood glucose control could be attributed to vitamin E (145). Another meta-analysis of trials found no effect of vitamins E and C, alone or in combination, on measures of β-cell function and insulin resistance (146). Yet, most studies were small and of short duration and thus did not assess the consequence of long-term use of antioxidant vitamins on the risk of vascular complications in diabetic patients. One 12-month randomized placebo-controlled trial in 456 participants with type 2 diabetes treated with metformin examined the effect of vitamin C (500 mg/day) or acetylsalicylic acid (aspirin; 100 mg/day) on risk factors for diabetes-related complications such as CVD (147). Both vitamin C and aspirin reduced fasting blood glucose and HbA1c concentrations and improved blood lipid profile in metformin-treated patients. Compared to placebo, both treatments were found to be more likely to limit risk factors contributing to diabetes-related complications, as well as to lower the risk of future cardiovascular events over a 10-year period (estimated using the Framingham risk score) (147).

Of note, it is possible that genetic differences among diabetic patients influence the effect of vitamin C supplementation on cardiovascular risk. In particular, a specific allele of the haptoglobin gene (Hp), namely Hp2, appears to be associated with an increased risk of diabetic vascular complications. Carriers of two copies of the Hp2 allele (Hp2-2) express a Hp protein that has a lower capacity to bind and remove pro-oxidant, free hemoglobin (Hb) from plasma, compared to Hp proteins coded by the Hp1-1 and Hp1-2 genotypes. When the results of the Women's Antioxidant Vitamin Estrogen (WAVE) trial were reanalyzed based on Hp genotype, antioxidant therapy (1,000 mg/day of vitamin C + 800 IU/day of vitamin E) was associated with improvement of coronary atherosclerosis in diabetic women with Hp1-1 genotype but worsening of coronary atherosclerosis in those carrying the Hp2-2 genotype (148). Results from another study by the same investigators suggested that vitamin C could not prevent the oxidation of high-density lipoprotein (HDL)-cholesterol by glycated Hb-Hp2-2 complexes *in vitro* nor restore impaired HDL function in diabetic mice carrying the Hp2-2 genotype (149).

Sepsis

Sepsis and septic shock — defined as persistent sepsis-induced low blood pressure — are associated with elevated mortality rates in critically ill patients (150, 151). Because systemic inflammatory responses involve excessive oxidative stress, it has been suggested that providing antioxidant nutrients like vitamin C may improve the outcome of critically ill patients in intensive care units. In addition, hypovitaminosis C is common in critically ill patients, especially in those with septic shock, and persists despite enteral/parenteral nutritional therapy providing recommended amounts of vitamin C (152). Vitamin C requirements are likely to be increased in this population due to the hypermetabolic response driven by the systemic inflammatory reaction (152, 153). Intravenous administration of 50 mg or 200 mg of vitamin C per kg per day for 96 hours to patients with sepsis admitted in intensive care unit was found to correct vitamin C deficiency. Vitamin C also prevented the rise of Sequential Organ Failure Assessment (SOFA) and Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II scores — used to assess severity of illness and risk of mortality — observed in placebo-treated patients (154). Vitamin C infusion also lowered the concentration of markers of inflammation and endothelial injury in patients compared to placebo (154). In another randomized, double-blind, controlled trial in 28 critically ill patients with septic shock, infusion of 25 mg of vitamin C per kg every six hours for 72 hours significantly limited the requirement to vasopressor norepinephrine — decreasing both the dose and duration of treatment — and dramatically improved the 28-day survival rate (155). Similar results have been reported in septic patients given intravenous vitamin C (1.5 g/6 h), hydrocortisone (50 mg/6 h), and thiamin (200 mg/12 h) until hospital discharge. Compared to standard-of-care, this intervention cocktail more than halved the mean duration of vasopressor use (18.3 h versus 54.9 h) and reduced the odds of mortality by nearly 90% (156). Although intravenous vitamin C administration appears to be safe and well tolerated, there is a non-negligible risk of oxalate nephropathy (a rare cause of kidney failure) in these critically ill patients (157).

See also the section on Sepsis in the Symposium on Vitamin C — Part of the LPI's 9th International Conference on Diet and Optimum Health.

Cancer

Route of administration

Studies in the 1970s and 1980s conducted by Linus Pauling, Ewan Cameron, and colleagues suggested that large doses of vitamin C (10 g/day infused intravenously for 10 days followed by at least 10 g/day orally indefinitely) were helpful in increasing the survival time and improving the quality of life of terminal cancer patients (158). Controversy surrounding the efficacy of vitamin C in cancer treatment ensued, leading to the recognition that the route of vitamin C administration is critical (22, 159). Compared to orally administered vitamin C, intravenous vitamin C can result in 30 to 70-fold higher plasma vitamin C concentrations (25). Higher plasma concentrations achieved via intravenous vitamin C administration are comparable to those that are toxic to cancer cells in culture. The anticancer mechanism of intravenous vitamin C action is under investigation. It may involve the production of high levels of hydrogen peroxide, selectively toxic to cancer cells (22, 160-162), or the deactivation of hypoxia inducible factor, a prosurvival transcription factor that protects cancer cells from various forms of stress (159, 163, 164). Vitamin C likely also plays a role in the maintenance of genome integrity and in the protection against cellular transformation through regulating DNA and histone demethylating enzymes (see Function) (165).

Safety

Current evidence from controlled clinical trials indicates that intravenous vitamin C is generally safe and well tolerated in cancer patients. Of note, because intravenous administration of 80 g of vitamin C precipitated hemolytic anemia in two subjects with glucose-6-phosphate dehydrogenase deficiency, patients due to receive high-dose vitamin C infusion are systematically screened for this genetic disorder (166). Four phase I clinical trials in patients with advanced cancer found that intravenous administration of vitamin C at doses up to 1.5 g/kg of body weight (equivalent to about 100 g/day for an average weight [70 kg] person) and 70 to 80 g/m^2 was well tolerated and safe in pre-screened patients (167-170). A few observational studies in cancer patients undergoing chemotherapy and/or radiotherapy reported that complementary intravenous vitamin C treatment was associated with a reduction in treatment-associated side effects and an improved quality of life (171). A phase I study in nine patients with metastatic pancreatic cancer showed that millimolar concentrations of plasma vitamin C could be reached safely when administered in conjunction with the cancer chemotherapy drugs, gemcitabine and erlotinib (168).

Sensitivity to vitamin C

Retrospective in vitro colony formation assays revealed that patient leukemic cells displayed variable sensitivity to vitamin C treatment: leukemic cells from seven out of the nine patients who experienced a significant clinical benefit were sensitive to vitamin C *in vitro* (i.e., "responders"); the leukemic cells from the remaining six patients were not sensitive to vitamin C (i.e., "non-responders"). Thus, *in vitro* vitamin C sensitivity assays may provide predictive value for the clinical response to intravenous vitamin C treatment. The mechanisms underlying differential sensitivity to vitamin C are under investigation. *In vitro* experiments performed using 11 different cancer cell lines demonstrated that sensitivity to vitamin C correlated with the expression of catalase, an enzyme involved in the decomposition of hydrogen peroxide (172). Approximately one-half of the cell lines tested were resistant to vitamin C cytotoxicity, a response associated with high levels of catalase activity.

Sensitivity to vitamin C may also be determined by the expression of sodium-dependent vitamin C transporter-2 (SVCT-2), which transports vitamin C into cells (173). Higher SVCT-2 levels were associated with enhanced sensitivity to vitamin C in nine different breast cancer cell lines. Moreover, SVCT-2 was significantly expressed in 20 breast cancer tissue samples, but weakly expressed in normal tissues. Finally, mutations in genes coding for vitamin C-dependent TET demethylases, mutations that are common in cancer cells, may also contribute to resistance to vitamin C treatment (165).

Efficacy

Current evidence of the efficacy of intravenous vitamin C in cancer patients is limited to observational studies, uncontrolled interventions, and case reports (174, 175). There is a need for larger, longer-duration phase II clinical trials that test the efficacy of intravenous vitamin C in disease progression and overall survival (176).

See also the section on Cancer in the Symposium on Vitamin C — Part of the LPI's 9th International Conference on Diet and Optimum Health.

Common cold

The work of Linus Pauling stimulated public interest in the use of doses greater than 1 g/day of vitamin C to prevent the common cold (177). In the past 40 years, numerous placebo-controlled trials have examined the effect of vitamin C supplementation on the prevention and treatment of colds. A 2013 meta-analysis of 53 placebo-controlled trials evaluated the effect of vitamin C supplementation on the incidence, duration, or severity of the common cold when taken as a continuous daily supplement (43 trials) or as therapy upon onset of cold symptoms (10 trials) (178). Regarding the incidence of colds, a difference was observed between two groups of participants. Regular supplementation with vitamin C (0.25 to 2 g/day) did not reduce the incidence of colds in the general population (23 trials); however, in participants undergoing heavy physical stress (e.g., marathon runners, skiers, or soldiers in subarctic conditions), vitamin C supplementation halved the incidence of colds (5 trials). A benefit of regular vitamin C supplementation was also seen in the duration of colds, with a greater benefit in children than in adults: The pooled effect of vitamin C supplementation was a 14% reduction in cold duration in children and an 8% reduction in adults. Finally, no significant effect of vitamin C supplementation (1-8 g/day) was observed in therapeutic trials in which vitamin C was administered after cold symptoms occurred.

In addition, a 2013 systematic review by the same investigators identified only two small randomized, double-blind, placebo-controlled trials that examined the effect of vitamin C on the incidence of respiratory infection-induced asthma (179). One trial found that vitamin C supplementation (1 g/day) for 14 weeks reduced the risk of asthma attacks precipitated by respiratory infection. The other trial randomized subjects diagnosed with infection-related asthma to receive 5 g/day of vitamin C or a placebo for one week; a lower proportion of participants was found to present with bronchial hypersensitivity to histamine — which characterizes chronic asthma — in the vitamin C group compared to the control group (reviewed in 179). These observations need to be confirmed in larger, well-designed trials.

Asthma

A 2013 systematic review identified 11 randomized controlled studies that evaluated the effect of vitamin C on asthma (eight trials) or exercise-induced bronchoconstriction (three trials) (180). Exercise-induced bronchoconstriction is a transient narrowing of the airways that occurs after exercise and is indicated by a ≥10% decline in Forced Expiratory Volume in 1 second (FEV_1). In the three trials that included a total of 40 participants with exercise-induced bronchoconstriction, vitamin C administration before exercise (a 0.5-g dose on two subsequent days in one trial, a single dose of 2 g in the second trial, and 1.5 g daily for two weeks in the third trial) significantly reduced the exercise-induced decline in FEV_1. Among the five out of eight trials in asthmatic subjects that reported on FEV_1 outcomes, none found a difference between vitamin C supplementation and placebo (180).

Lead toxicity

Although the use of lead paint and leaded gasoline has been discontinued in the US, lead toxicity continues to be a significant health problem, especially in children living in urban areas. Abnormal growth and development have been observed in infants of women exposed to lead during pregnancy, while children who are chronically exposed to lead are more likely to develop learning disabilities, behavioral problems, and to have a low IQ. In adults, lead toxicity may result in kidney damage, high blood pressure, and anemia.

Several cross-sectional studies have reported an inverse association between vitamin C status and blood lead concentration. For instance, in a study of 747 older men, blood lead concentration was significantly higher in those who reported total dietary vitamin C intakes averaging less than 109 mg/day compared to those with higher vitamin C intakes (181). A much larger study of 19,578 people, including 4,214 children from 6 to 16 years of age, found higher serum vitamin C concentrations to be associated with significantly lower blood lead concentrations (182). A US national survey of more than 10,000 adults found that blood lead concentrations were inversely related to serum vitamin C concentrations (183).

Cigarette smoking or second-hand exposure to cigarette smoke contributes to increased blood lead concentration and a state of chronic low-level lead exposure. An intervention trial in 75 adult male smokers found that supplementation with 1,000 mg/day of vitamin C resulted in significantly lower blood lead concentration over a four-week treatment period compared to placebo (184). A lower dose of 200 mg/day did not significantly affect blood lead concentration, although serum vitamin C concentrations were not different from those in the group who took 1,000 mg/day.

The mechanism(s) by which vitamin C reduces blood lead concentration is not known, yet it has been proposed that vitamin C could inhibit intestinal absorption (184) or enhance urinary excretion of lead (185).

Sources

Unlike plants and most animals, humans have lost the ability to synthesize vitamin C endogenously and therefore have an essential dietary requirement for this vitamin (see The Recommended Dietary Allowance). Results from 7,277 participants in the US National Health and Nutrition Examination Survey (NHANES) 2003-2004 indicated that an estimated 7.1% of individuals ages ≥6 years were deficient in vitamin C — based on serum vitamin C concentrations <11.4 μmol/L (36). The national study identified smokers and those of lower socioeconomic status to both be at higher risk for vitamin C deficiency (36).

Food sources

As shown in **Table 3**, different fruit and vegetables vary in their vitamin C content, but five servings (2½ cup-equivalents) of a variety of fruit and vegetables should average out to about 150 to 200 mg of vitamin C, especially if vitamin C-rich fruits are consumed. If you wish to check foods for their vitamin C content, search USDA's FoodData Central.

Table 3. Some Food Sources of Vitamin C

Food	Serving	Vitamin C (mg)
Kiwifruit, Zespri SunGold	1 fruit (81 g)	131
Grapefruit juice, pink, raw	¾ cup (6 ounces)	94
Orange juice, raw	¾ cup (6 ounces)	93
Strawberries	1 cup, whole	85
Grapefruit juice, white, raw	¾ cup (6 ounces)	70
Kiwifruit	1 fruit (74 g)	69
Orange	1 medium	65
Sweet red pepper, raw	½ cup, chopped	59
Broccoli, cooked	½ cup	51
Grapefruit, raw	½ medium	44
Brussel sprouts, cooked	½ cup	37
Potato, white, flesh and skin	1 medium, baked	22
Tomato, red, ripe, raw	1 medium	17
Banana, raw	1 medium	10
Apple, raw	1 medium	8
Spinach, raw	1 cup	8

Supplements

Vitamin C (L-ascorbic acid) is available in many forms, but there is little scientific evidence that any one form is better absorbed or more effective than another. Most experimental and clinical research uses ascorbic acid or its sodium salt, called sodium ascorbate. Natural and synthetic L-ascorbic acid are chemically identical and there are no known differences regarding biological activities or bioavailability (186).

Mineral ascorbates

Mineral salts of vitamin C are considered less acidic than vitamin C and therefore are considered "buffered." Some people find them less irritating to the gastrointestinal tract than ascorbic acid. Sodium ascorbate and calcium ascorbate are the most common forms, although a number of other mineral ascorbates are available. Sodium ascorbate provides 111 mg of sodium (889 mg of ascorbic acid) per 1,000 mg of sodium ascorbate, and calcium ascorbate generally provides 90 to 110 mg of calcium (890-910 mg of ascorbic acid) per 1,000 mg of calcium ascorbate.

Vitamin C with flavonoids

Flavonoids are a class of water-soluble plant pigments that are often found in vitamin C-rich fruit and vegetables, especially citrus fruit and berries (see the article on Flavonoids). There is little evidence that the flavonoids in most commercial preparations increase the bioavailability or efficacy of vitamin C (187). Some, yet not all, studies in animal models such as vitamin C-deficient guinea pigs or genetically scorbutic rats found an increased uptake of vitamin C in peripheral circulation and specific organs in the presence of flavonoids. However, studies conducted in humans found no differences in bioavailability of vitamin C from flavonoid-rich whole fruit or fruit juice and synthetic vitamin C (reviewed in 186).

Vitamin C and metabolites

One supplement, Ester-C®, contains mainly calcium ascorbate and includes small amounts of the vitamin C metabolites, dehydroascorbic acid (oxidized ascorbic acid), calcium threonate, and trace amounts of xylonate and lyxonate. Although these metabolites are purported to increase the bioavailability of vitamin C, the only published study in humans addressing this issue found no difference between Ester-C® and commercially available vitamin C tablets with respect to the absorption and urinary excretion of vitamin C (187). Ester-C® should not be confused with ascorbyl palmitate, which is also marketed as "vitamin C ester" (see below).

Ascorbyl palmitate

Ascorbyl palmitate is a vitamin C ester (i.e., ascorbic acid linked to a fatty acid). In this case, vitamin C is esterified to the saturated fatty acid, palmitic acid, resulting in a fat-soluble form of vitamin C. Ascorbyl palmitate has been added to a number of skin creams due to interest in its antioxidant properties, as well as its importance in collagen synthesis (see the separate article, Vitamin C and Skin Health) (188). Although ascorbyl palmitate is also available as an oral supplement, most of it is likely hydrolyzed to ascorbic acid and palmitic acid in the digestive tract before it is absorbed (189). Ascorbyl palmitate is marketed as "vitamin C ester," which should not be confused with Ester-C® (see above).

Other formulations of vitamin C

One small placebo-controlled, cross-over trial in 11 men showed that the oral administration of 4 g of vitamin C resulted in a greater vitamin C concentration in plasma over a four-hour period when vitamin C was encapsulated in liposomes compared to unencapsulated vitamin C (190). Although liposomal encapsulation could increase vitamin C bioavailability, plasma vitamin C concentrations were much lower than those achieved with intravenous vitamin C administration (190).

For a more detailed review of scientific research on the bioavailability of different forms of vitamin C, see The Bioavailability of Different Forms of Vitamin C.

Safety

Toxicity

A number of possible adverse health effects of very large doses of vitamin C have been identified, mainly based on *in vitro* experiments or isolated case reports, and include genetic mutations, birth defects, cancer, atherosclerosis, kidney stones, "rebound scurvy," increased oxidative stress, excess iron absorption, vitamin B_{12} deficiency, and erosion of dental enamel. However, none of these alleged adverse health effects have been confirmed in subsequent studies, and there is no reliable scientific evidence that doses of vitamin C up to 10 g/day in adults are toxic or detrimental to health. The concern of kidney stone formation with vitamin C supplementation is discussed below.

With the latest RDA published in 2000, a tolerable upper intake level (UL) for vitamin C was set for the first time (**Table 4**). A UL of 2 g (2,000 mg) daily was recommended in order to prevent generally healthy adults from experiencing diarrhea and gastrointestinal disturbances (35). Such symptoms are not generally serious, especially if they resolve with temporary discontinuation of vitamin C supplementation.

Table 4. Tolerable Upper Intake Level (UL) for Vitamin C

Age Group	UL (mg/day)
Infants 0-12 months	Not possible to establish*
Children 1-3 years	400
Children 4-8 years	650
Children 9-13 years	1,200
Adolescents 14-18 years	1,800
Adults 19 years and older	2,000
*Source of intake should be from foods or formula only.	

Kidney stones

Because oxalate is a metabolite of vitamin C, there is some concern that high vitamin C intake could increase the risk of calcium oxalate kidney stones. Some (24, 191, 192), but not all (193-195), studies have reported that supplemental vitamin C increases urinary oxalate concentrations. Whether any increase in oxalate levels would translate to an elevation in risk for kidney stones has been examined in several epidemiological studies. Two large prospective cohort studies, one following 45,251 men for six years and the other following 85,557 women for 14 years, reported that consumption of ≥1,500 mg of vitamin C daily did not increase the risk of kidney stone formation compared to those consuming <250 mg daily (196, 197). On the other hand, two other large prospective studies reported that a high intake of vitamin C was associated with an increased risk of kidney stone formation in men (198, 199). Specifically, the Health Professionals Follow-Up Study collected data on dietary and supplemental vitamin C intake every four years in 45,619 male health professionals (ages 40-75 years) (198). After 14 years of follow-up, it was found that men who consumed ≥1,000 mg/day of vitamin C had a 41% higher risk of kidney stones compared to men consuming <90 mg of vitamin C daily. In the Cohort of Swedish Men study, self-reported use of single-nutrient vitamin C supplements (taken seven or more times per week) at baseline was associated with a two-fold higher risk of incident kidney stones among 48,840 men (ages 45-79 years) followed for 11 years (199). Despite conflicting results, it may be prudent for individuals predisposed to oxalate kidney stone formation to avoid high-dose vitamin C supplementation.

Drug interactions

Overall, evidence suggesting specific drugs can lower blood vitamin C concentrations in humans is limited. Dihydropyridine calcium channel blockers (e.g., nicardipine, nifedipine) can inhibit vitamin C uptake by intestinal cells *in vitro*. However, a reduction in blood vitamin C concentrations with these drugs has not been reported in humans (200). Aspirin can impair vitamin C status if taken frequently (201).

Conversely, there are case reports suggesting that supplemental vitamin C may lower blood concentrations of some medications, such as fluphenazine (the antipsychotic drug, Prolixin) and indinavir (the antiretroviral drug, Crixivan) (200). There is some evidence, though controversial, that vitamin C interacts with anticoagulant medications like warfarin (Coumadin). Large doses of vitamin C may block the action of warfarin and thus lower its effectiveness. Individuals on anticoagulants should limit their vitamin C intake to <1 g/day and have their prothrombin time monitored by the clinician following their anticoagulant therapy (200). In addition, vitamin C may bind aluminum in the gut and increase the absorption of aluminum-containing compounds (e.g., aluminum-containing antacids, aluminum-containing phosphate binders). People with impaired kidney function may be at risk for aluminum toxicity when supplemental vitamin C is taken at the same time as these compounds (200, 201). Finally, supplemental vitamin C may increase blood estrogen concentrations in women using oral contraceptives or hormone replacement therapy (200).

The potential effect of antioxidants during chemotherapy is not well understood, yet only likely to be an issue if a specific chemotherapeutic agent acts through an oxidative mechanism, which is uncommon (171). It is not clear whether vitamin C given parenterally could diminish or increase the efficacy of chemotherapy drugs — in particular, akylating agents (e.g., cyclophosphamide, busulfan), antitumor antibiotics (e.g., doxorubicin, bleomycin), and arsenic trioxide. Patients are advised to discuss with their oncologist before using vitamin C supplements (200, 201).

Because high doses of vitamin C have also been found to interfere with the interpretation of certain laboratory tests (e.g., serum bilirubin, serum creatinine, and the stool guaiac assay for occult blood), it is important to inform one's health care provider of any recent supplement use.

Antioxidant supplements and HMG-CoA reductase inhibitors (statins)

A three-year randomized controlled trial in 160 patients with documented coronary heart disease and low blood HDL concentrations found that a combination of simvastatin (Zocor) and niacin increased HDL concentration, inhibited the progression of coronary artery stenosis (narrowing), and decreased the frequency of cardiovascular events, such as myocardial infarction and stroke (202). Surprisingly, when an antioxidant combination (1,000 mg vitamin C, 800 IU vitamin E, 100 μg selenium, and 25 mg β-carotene daily) was taken with the simvastatin-niacin combination, the protective effects were diminished. Since the antioxidants were taken together in this trial, the individual contribution of vitamin C cannot be determined. In contrast, a much larger trial in more than 20,000 men and women with coronary heart disease or diabetes mellitus found that simvastatin and an antioxidant combination (600 mg vitamin E, 250 mg vitamin C, and 20 mg β-carotene daily) did not diminish the cardioprotective effects of simvastatin therapy over a five-year period (203). These contradictory findings indicate that further research is needed on potential interactions between antioxidant supplements and cholesterol-lowering drugs, such as HMG-CoA reductase inhibitors (statins).

Does vitamin C promote oxidative damage under physiological conditions?

Vitamin C is known to function as a highly effective antioxidant in living organisms. However, in test tube experiments, vitamin C can interact with some free metal ions and lead to the generation of potentially damaging free radicals. Although free metal ions are not generally found under physiological conditions, the idea that high doses of vitamin C might be able to promote oxidative damage *in vivo* has received a great deal of attention. Widespread publicity has been given to a few studies suggesting a pro-oxidant effect of vitamin C (204, 205), but these studies turned out to be either flawed or of no physiological relevance. A comprehensive review of the literature found no credible scientific evidence that supplemental vitamin C promotes oxidative damage under physiological conditions or in humans (206).

Linus Pauling Institute Recommendation

Combined evidence from metabolic, pharmacokinetic, and observational studies, and from randomized controlled trials supports consuming sufficient vitamin C to achieve plasma concentrations of at least 60 μmol/L. While most generally healthy young adults can achieve these plasma concentrations with daily vitamin C intake of at least 200 mg/day, some individuals may have a lower vitamin C absorptive capacity than what is currently documented. Thus, the Linus Pauling Institute recommends a vitamin C intake of 400 mg daily for adults to ensure replete tissue concentrations (29) — an amount substantially higher than the RDA yet with minimal risk of side effects.

This recommendation can be met through food if the diet includes at least several servings of vitamin C-rich fruit and vegetables (e.g., citrus fruit, kiwifruit, peppers; see Food sources) as part of the daily recommended fruit and vegetable intake (see article on Fruit and Vegetables). Most multivitamin supplements provide at least 60 mg of vitamin C.

Older adults (>50 years)

Whether older adults have higher requirements for vitamin C is not yet known with certainty, yet some older populations have been found to have vitamin C intakes considerably below the RDA of 75 and 90 mg/day for women and men, respectively (207). A vitamin C intake of at least 400 mg daily may be particularly important for older adults who are at higher risk for age-related chronic diseases. Pharmacokinetic studies in older adults have not yet been conducted, but there is some evidence suggesting that the efficiency of one of the molecular mechanisms for the cellular uptake of vitamin C declines with age (208). Because maximizing blood concentrations of vitamin C may be important in protecting against oxidative damage to cells and biological molecules, a vitamin C intake of at least 400 mg daily might benefit older adults who are at higher risk for chronic diseases caused, in part, by oxidative damage, such as heart disease, stroke, certain cancers, and cataract.

For more information on the difference between Dr Linus Pauling's recommendation and the Linus Pauling Institute's recommendation for vitamin C intake, select the highlighted text.

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Supplemental Forms

Español

The Bioavailability of Different Forms of Vitamin C (Ascorbic Acid)

In the rapidly expanding market of dietary supplements, it is possible to find vitamin C in many different forms with many claims regarding its efficacy or bioavailability. Bioavailability refers to the degree to which a nutrient (or drug) becomes available to the target tissue after it has been administered. We reviewed the literature for the results of scientific research on the bioavailability of different forms of vitamin C.

Natural vs. synthetic ascorbic acid

Natural and synthetic L-ascorbic acid are chemically identical, and there are no known differences in their biological activity. The possibility that the bioavailability of L-ascorbic acid from natural sources might differ from that of synthetic ascorbic acid was investigated in at least two human studies, and no clinically significant differences were observed. A study of 12 males (6 smokers and 6 nonsmokers) found the bioavailability of synthetic ascorbic acid (powder administered in water) to be slightly superior to that of orange juice, based on blood levels of ascorbic acid, and not different based on ascorbic acid in leukocytes (white blood cells) (1). A study in 68 male nonsmokers found that ascorbic acid consumed in cooked broccoli, orange juice, orange slices, and as synthetic ascorbic acid tablets are equally bioavailable, as measured by plasma ascorbic acid levels (2, 3).

Different forms of ascorbic acid

The gastrointestinal absorption of ascorbic acid occurs through an active transport process, as well as through passive diffusion. At low gastrointestinal concentrations of ascorbic acid active transport predominates, while at high gastrointestinal concentrations active transport becomes saturated, leaving only passive diffusion. In theory, slowing down the rate of stomach emptying (e.g., by taking ascorbic acid with food or taking a slow-release form of ascorbic acid) should increase its absorption. While the bioavailability of ascorbic acid appears equivalent whether it is in the form of powder, chewable tablets, or non-chewable tablets, the bioavailability of ascorbic acid from slow-release preparations is less certain.

A study of three men and one woman found 1 gram of ascorbic acid to be equally well absorbed from solution, tablets, and chewable tablets, but the absorption from a timed-release capsule was 50% lower. Absorption was assessed by measuring urinary excretion of ascorbic acid after an intravenous dose of ascorbic acid and then comparing it to urinary excretion after the oral dosage forms (4).

A more recent study examined the plasma levels of ascorbic acid in 59 male smokers supplemented for two months with either 500 mg/day of slow-release ascorbic acid, 500 mg/day of plain ascorbic acid, or a placebo. After two months of supplementation no significant differences in plasma ascorbic acid levels between the slow-release and plain ascorbic acid groups were found (5). A second placebo-controlled trial also evaluated plain ascorbic acid versus slow-release ascorbic acid in 48 male smokers (6). Participants were supplemented with either 250 mg plain ascorbic acid, 250 mg slow-release ascorbic acid, or placebo twice daily for four weeks. No differences were observed in the change in plasma ascorbate concentration or area under the curve following ingestion of either formulation.

Mineral ascorbates

Mineral salts of ascorbic acid (mineral ascorbates) are less acidic, and therefore, considered "buffered." Thus, mineral ascorbates are often recommended to people who experience gastrointestinal problems (upset stomach or diarrhea) with plain ascorbic acid. There appears to be little scientific research to support or refute the claim that mineral ascorbates are less irritating to the gastrointestinal tract. When mineral salts of ascorbic acid are taken, both the ascorbic acid and the mineral appear to be well absorbed, so it is important to consider the dose of the mineral accompanying the ascorbic acid when taking large doses of mineral ascorbates. For the following discussion, it should be noted that 1 gram (g)= 1,000 milligrams (mg) and 1 milligram (mg) = 1,000 micrograms (μg). Mineral ascorbates are available in the following forms:

- **Sodium ascorbate:** 1,000 mg of sodium ascorbate generally contains 111 mg of sodium. Individuals following low-sodium diets (e.g., for high blood pressure) are generally advised to keep their total dietary sodium intake to less than 2,500 mg/day. Thus, megadoses of vitamin C in the form of sodium ascorbate could significantly increase sodium intake (see Sodium Chloride).
- **Calcium ascorbate:** Calcium ascorbate generally provides 90-110 mg of calcium (890-910 mg of ascorbic acid) per 1,000 mg of calcium ascorbate. Calcium in this form appears to be reasonably well absorbed. The recommended dietary calcium intake for adults is 1,000 to 1,200 mg/day. Total calcium intake should not exceed the UL, which is 2,500 mg/day for adults aged 19-50 years and 2,000 mg/day for adults older than 50 years (see Calcium).

The following mineral ascorbates are more likely to be found in combination with other mineral ascorbates, as well as other minerals. It's a good idea to check the labels of dietary supplements for the ascorbic acid dose as well as the dose of each mineral. Recommended dietary intakes and maximum upper levels of intake (when available) are listed after the individual mineral ascorbates below:

- **Potassium ascorbate:** The minimal requirement for potassium is thought to be between 1.6 and 2.0 g/day. Fruit and vegetables are rich sources of potassium, and a diet rich in fruit and vegetables may provide as much as 8 to 11 g/day. Acute and potentially fatal potassium toxicity (hyperkalemia) is thought to occur at a daily intake of about 18 g/day of potassium in adults. Individuals taking potassium-sparing diuretics and those with renal insufficiency (kidney failure) should avoid significant intake of potassium ascorbate. The purest form of commercially available potassium ascorbate contains 0.175 grams (175 mg) of potassium per gram of ascorbate (see Potassium).
- **Magnesium ascorbate:** The recommended dietary allowance (RDA) for magnesium is 400-420 mg/day for adult men and 310-320 mg/day for adult women. The upper level (UL) of intake for magnesium from supplements should not exceed 350 mg/day (see Magnesium).
- **Zinc ascorbate:** The RDA for zinc is 11 mg/day for adult men and 8 mg/day for adult women. The upper level (UL) of zinc intake for adults should not exceed 40 mg/day (see Zinc).
- **Molybdenum ascorbate:** The RDA for molybdenum is 45 micrograms (μg)/day for adult men and women. The upper level (UL) of molybdenum intake for adults should not exceed 2,000 μg (2 mg)/day (see Molybdenum).
- **Chromium ascorbate:** The recommended dietary intake (AI) for chromium is 30-35 μg/day for adult men and 20-25 μg/day for adult women. A maximum upper level (UL) of intake has not been determined by the US Food and Nutrition Board (see Chromium).
- **Manganese ascorbate:** The recommended dietary intake (AI) for manganese is 2.3 mg/day for adult men and 1.8 mg/day for adult women. The upper level (UL) of intake for manganese for adults should not exceed 11 mg/day. Manganese ascorbate is found in some preparations of glucosamine and chondroitin sulfate, and following the recommended dose on the label of such supplements could result in a daily intake exceeding the upper level for manganese (see Manganese).

Vitamin C with bioflavonoids

Bioflavonoids or flavonoids are polyphenolic compounds found in plants. Vitamin C-rich fruit and vegetables, especially citrus fruit, are often rich sources of flavonoids as well. The effect of bioflavonoids on the bioavailability of ascorbic acid has been recently reviewed (7).

Results from the 10 clinical studies comparing the absorption of vitamin C alone or vitamin C in flavonoid-containing foods showed no appreciable differences in bioavailability of ascorbic acid. Only one study, which included five men and three women, found that a 500-mg supplement of synthetic ascorbic acid, given in a natural citrus extract containing bioflavonoids, proteins, and carbohydrates, was more slowly absorbed and 35% more bioavailable than synthetic ascorbic acid alone, when based on plasma levels of ascorbic acid (8). The remaining studies showed either no change or slightly lower plasma ascorbate levels in subjects who consumed vitamin C with flavonoids compared to flavonoids alone (7).

Another assessment of vitamin C bioavailability is measuring urinary ascorbate levels to approximate rates of vitamin C excretion. One study in six young Japanese males (22-26 years old) showed a significant reduction in urinary excretion of ascorbic acid in the presence of acerola juice, a natural source of both vitamin C and flavonoids (9). However, three separate studies showed that urinary levels of vitamin C were increased after consumption of kiwifruit (10), blackcurrant juice (11), or orange juice (1). Overall, the impact of flavonoids on the bioavailability of vitamin C seems to be negligible; however, there is a need for carefully controlled studies using specific flavonoid extracts (7).

Ascorbate and vitamin C metabolites (Ester-C®)

Ester-C® contains mainly calcium ascorbate, but also contains small amounts of the vitamin C metabolites, dehydroascorbic acid (oxidized ascorbic acid), calcium threonate, and trace levels of xylonate and lyxonate. In their literature, the manufacturers state that the metabolites, especially threonate, increase the bioavailability of the vitamin C in this product, and they indicate that they have performed a study in humans that demonstrates the increased bioavailability of vitamin C in Ester-C®. This study has not been published in a peer-reviewed journal. A small published study of vitamin C bioavailability in eight women and one man found no difference between Ester-C® and commercially available ascorbic acid tablets with respect to the absorption and urinary excretion of vitamin C (12). Ester-C® should not be confused with ascorbyl palmitate, which is also marketed as "vitamin C ester" (see below).

Ascorbyl palmitate

Ascorbyl palmitate is a fat-soluble antioxidant used to increase the shelf life of vegetable oils and potato chips (13). It is an amphipathic molecule, meaning one end is water-soluble and the other end is fat-soluble. This dual solubility allows it to be incorporated into cell membranes. When incorporated into the cell membranes of human red blood cells, ascorbyl palmitate has been found to protect them from oxidative damage and to protect α-tocopherol (a fat-soluble antioxidant) from oxidation by free radicals (14). However, the protective effects of ascorbyl palmitate on cell membranes have only been demonstrated in the test tube. Taking ascorbyl palmitate orally probably doesn't result in any significant incorporation into cell membranes because most of it appears to be hydrolyzed (broken apart into palmitate and ascorbic acid) in the human digestive tract before it is absorbed. The ascorbic acid released by the hydrolysis of ascorbyl palmitate appears to be as bioavailable as ascorbic acid alone (15). The presence of ascorbyl palmitate in oral supplements contributes to the ascorbic acid content of the supplement and probably helps protect fat-soluble antioxidants in the supplement. The roles of vitamin C in promoting collagen synthesis and as an antioxidant have generated interest in its use on the skin (see the article, Vitamin C and Skin Health). Ascorbyl palmitate is frequently used in topical preparations because it is more stable than some aqueous (water-soluble) forms of vitamin C (16). Ascorbyl palmitate is also marketed as vitamin C ester," which should not be confused with Ester-C® (see above).

D-Isoascorbic acid (Erythorbic acid)

Erythorbic acid is an isomer of ascorbic acid. Isomers are compounds that have the same kinds and numbers of atoms, but different molecular arrangements. The difference in molecular arrangement among isomers may result in different chemical properties. Erythorbic acid is used in the US as an antioxidant food additive and is generally recognized as safe. It has been estimated that more than 200 mg erythorbic acid per capita is introduced daily into the US food system. Unlike ascorbic acid, erythorbic acid does not appear to exert vitamin C activity, for example, it did not prevent scurvy in guinea pigs (one of the few animal species other than humans that does not synthesize ascorbic acid). However, guinea pig studies also indicated that increased erythorbic acid intake reduced the bioavailability of ascorbic acid by up to 50%. In contrast, a series of studies in young women found that up to 1,000 mg/day of erythorbic acid for as long as 40 days was rapidly cleared from the body and had little effect on the bioavailability of ascorbic acid, indicating that erythorbic acid does not diminish the bioavailability of ascorbic acid in humans at nutritionally relevant levels of intake (17).

Other formulations of vitamin C

PureWay-C® is composed of vitamin C and lipid metabolites. Two cell culture studies using PureWay-C® have been published by the same investigators (18, 19), but *in vivo* data are currently lacking. A small study in healthy adults found that serum levels of vitamin C did not differ when a single oral dose (1 gram) of either PureWay-C® or ascorbic acid was administered (20).

Another formulation of vitamin C, liposomal-encapsulated vitamin C (e.g., Lypo-spheric™ vitamin C) is now commercially available. One report suggested that liposomal-encapsulated vitamin C may be better absorbed than the vitamin in a non-encapsulated form (21).

Large-scale, pharmacokinetic studies are needed to determine how the bioavailability of these vitamin C formulations compares to that of ascorbic acid.

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Pauling Recommendation

Difference Between Dr. Linus Pauling's Recommendations and the LPI's Recommendation for Vitamin C Intake

Dr. Pauling, for whom the Linus Pauling Institute has great respect, based his own recommendations for vitamin C largely on theoretical arguments. In developing his recommendations, he used cross-species comparisons, evolutionary arguments, the concept of biochemical individuality, and the amount of vitamin C likely consumed in a raw plant food diet. Using this approach, Dr. Pauling suggested in the early 1970s that the optimum daily intake may be about 2,000 milligrams of vitamin C and that everyone should get at least 200 to 250 mg/day. In a 1974 radio interview, he noted that "the first 250 mg is more important than any later 250 mg. The first 250 mg leads you up to the level where the blood is saturated. You can achieve a higher volume [concentration] in the blood by a larger intake, but you get much better improvement for the first 250 mg than for additional grams." Dr. Pauling significantly increased his recommendation in his 1986 book *How To Live Longer and Feel Better*. At the Linus Pauling Institute, we have based our vitamin C recommendations on the current body of scientific evidence, which is significantly greater than it was at Pauling's time but remains incomplete owing to the many diverse functions of vitamin C in the human body that have yet to be fully understood.

In this context, it is important to note that data from the National Institutes of Health (NIH) have indicated that vitamin C levels in plasma and circulating cells become fully saturated at intakes of about 400 mg/day in young, healthy nonsmokers. These observations are consistent with other data that intakes of about 400 mg/day are associated with reduced risk of heart disease. While these NIH studies are the best we currently have regarding the pharmacokinetics of vitamin C in the human body, they have numerous limitations, including the fact that they are based on a small number of young, healthy men and women. We currently do not know how much vitamin C is required to achieve saturation of cells and tissues in children, older adults, and diseased or stressed individuals. A meta-analysis of 36 studies on the relationship between vitamin C intake and plasma concentrations found that the elderly require a substantially higher daily intake of vitamin C to attain plasma concentrations that younger adults achieve at a lower intake. Additionally, work by Linus Pauling Institute investigators has shown that cellular uptake of vitamin C declines with age, supporting the notion that vitamin C requirements are increased in the elderly.

Therefore, the Linus Pauling Institute's intake recommendation of 400 mg/day of vitamin C for generally healthy adults takes into account the currently available epidemiological, biochemical, and clinical evidence, while acknowledging the extremely low toxicity of vitamin C and the incomplete information regarding optimum intake. It should also be noted that the Linus Pauling Institute's recommendation is strictly directed towards prevention of disease in healthy individuals, not treatment of disease. Thus, individuals suffering from certain diseases may require substantially larger amounts of vitamin C to achieve optimum body levels or derive therapeutic benefits, areas that were of great interest to Linus Pauling and need to be further explored.

Vitamin D

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Summary

- Vitamin D can be synthesized in the skin upon exposure to sunlight and is then metabolized in the liver and kidney to the metabolically active form called 1α,25-dihydroxyvitamin D. Through binding to the vitamin D receptor (VDR), 1α,25-dihydroxyvitamin D can regulate the expression of hundreds of genes involved in skeletal and other biological functions. *(More information)*
- Vitamin D is essential for maintenance of bone mineralization through the regulation of calcium and phosphorus homeostasis. Vitamin D also exhibits many non-skeletal effects, particularly on the immune, endocrine, and cardiovascular systems. *(More information)*
- Vitamin D is important for normal bone development and maintenance. Severe vitamin D deficiency causes rickets in children and osteomalacia in adults. *(More information)*
- Secondary hyperparathyroidism due to vitamin D insufficiency can increase bone breakdown and precipitate osteoporosis. Randomized clinical trials indicate that supplementation with at least 800 IU/day of vitamin D may reduce the risk of falls and fractures in older individuals. *(More information)*
- Vitamin D can regulate cell differentiation and growth by binding to the vitamin D receptor found in most body cells. Observational studies have reported associations between low sun exposure, poor vitamin D status, and increased risk of developing colorectal and breast cancer. Randomized controlled trials are needed to evaluate whether cancer prevention may benefit from vitamin D supplementation. *(More information)*
- Various observational studies have reported inverse associations between vitamin D status and the susceptibility or severity of autoimmune diseases, including type 1 diabetes mellitus, multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus. *(More information)*
- Current evidence from observational studies suggests an inverse relationship between circulating vitamin D concentrations and risk of type 2 diabetes mellitus. It is not yet known whether correcting vitamin D deficiency in individuals with glucose intolerance can decrease the risk of progression to type 2 diabetes mellitus. *(More information)*
- Randomized clinical trials are currently investigating whether vitamin D supplementation can limit cognitive deterioration and disease progression in subjects with neurodegenerative disease. *(More information)*
- Vitamin D insufficiency in pregnant women may be associated with several adverse effects for the mother and newborn. Safety and benefits of vitamin D supplementation during pregnancy both need to be evaluated in clinical trials. *(More information)*
- Observational studies have documented an association between vitamin D deficiency and increased incidence and severity of the coronavirus disease, COVID-19. *(More information)*
- Preliminary studies have shown that vitamin D supplementation may offer promising improvements in the management of atopic dermatitis (eczema) and Crohn's disease. *(More information)*

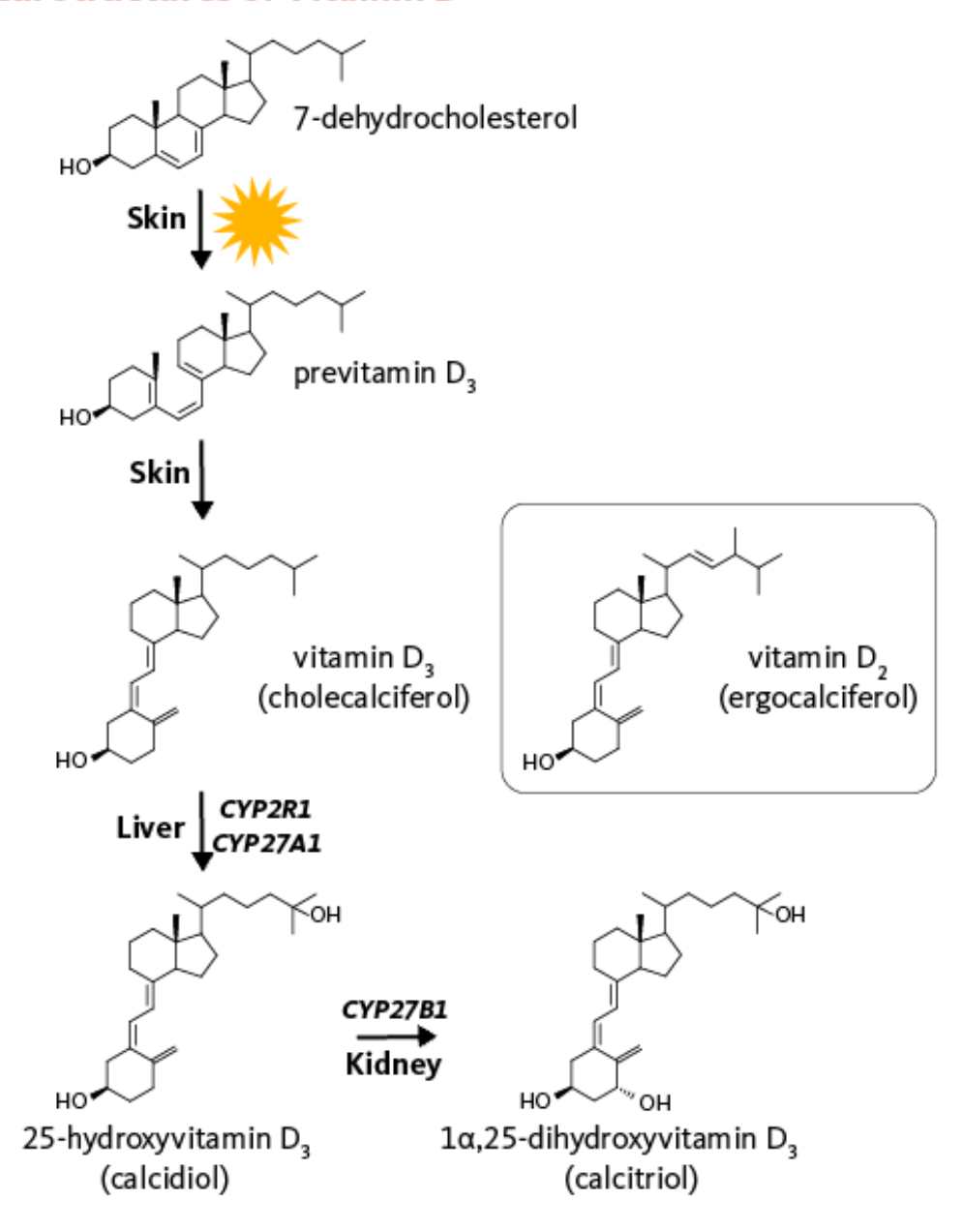
Vitamin D is a fat-soluble vitamin that regulates calcium homeostasis and is vital for bone health (1). While it can also be obtained from dietary sources or supplements, vitamin D_3 (cholecalciferol) is synthesized in the human skin from 7-dehydrocholesterol upon exposure to ultraviolet-B (UVB) radiation from sunlight (see the separate article on Vitamin D and Skin Health). Vitamin D_2 (ergocalciferol) is a vitamin D analog photosynthesized in plants, mushrooms, and yeasts; vitamin D_2 is also sometimes used in vitamin D food fortification (2). When vitamin D_3 in skin is inadequate due to insufficient exposure to UVB radiation, oral intake of vitamin D is necessary to meet vitamin D requirements.

Function

Vitamin D metabolism

Cholecalciferol and ergocalciferol are biologically inactive precursors of vitamin D and must be converted to biologically active forms in the liver and kidneys (**Figure 1**). Indeed, following dietary intake or synthesis in the epidermis of skin after UVB exposure, both forms of vitamin D enter the circulation and are transported to the liver by the vitamin D-binding protein (and to a lesser extent by albumin). In hepatocytes (liver cells), vitamin D is hydroxylated to form 25-hydroxyvitamin D (calcidiol; calcifediol). Exposure to sunlight or dietary intake of vitamin D increases serum concentrations of 25-hydroxyvitamin D. 25-Hydroxyvitamin D constitutes the major circulating form of vitamin D, and the sum of 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 concentrations in serum is used as an indicator of vitamin D nutritional status (3). The renal 25-hydroxyvitamin D_3-1α-hydroxylase enzyme (also known as CYP27B1) eventually catalyzes a second hydroxylation that converts 25-hydroxyvitamin D to 1α,25-dihydroxyvitamin D (calcitriol). The production of 1α,25-dihydroxyvitamin D in the kidneys is regulated by several factors, including serum phosphorus, calcium, parathyroid hormone (PTH), fibroblast growth factor-23 (FGF-23), and 1α,25-dihydroxyvitamin D itself. While the kidney is the main source of 1α-hydroxylase activity, extra-renal production of 1α,25-dihydroxyvitamin D has also been demonstrated in a variety of tissues, including skin, parathyroid gland, breast, colon, prostate, as well as cells of the immune system and bone cells (2). Most of the physiological effects of vitamin D in the body are related to the activity of 1α,25-dihydroxyvitamin D (4). Various forms of vitamin D are listed in **Figure 1**.

Figure 1. Chemical Structures of Vitamin D


7-dehydrocholesterol
HO
Skin
previtamin D_3
HO
Skin
vitamin D_3 (cholecalciferol)
HO
vitamin D_2 (ergocalciferol)
HO
Liver
CYP2R1
CYP27A1
OH
HO
25-hydroxyvitamin D_3 (calcidiol)
CYP27B1
Kidney
OH
HO
OH
1α,25-dihydroxyvitamin D_3 (calcitriol)

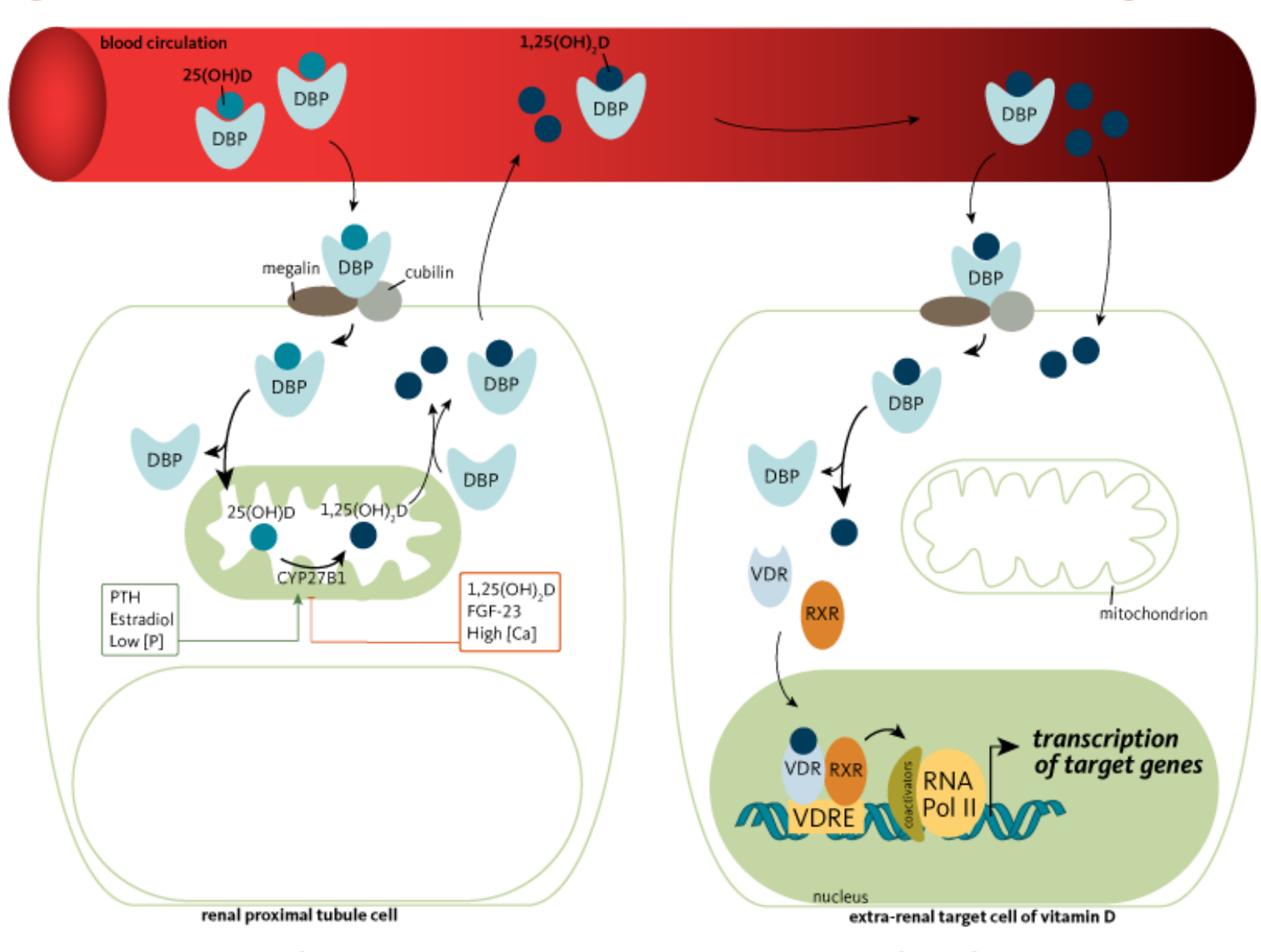
Vitamin D synthesis. Previtamin D_3 is synthesized in the upper layers of the skin from 7-dehydrocholesterol by the action of ultraviolet light (UVB). A nonenzymatic conversion of previtamin D_3 into vitamin D_3 (cholecalciferol) then occurs in lower layers of the skin. Vitamin D_3 is quickly transported to adipose tissue for storage or liver for activation. In liver cells, several cytochrome P450 (CYP) enzymes can catalyze the 25-hydroxylation of vitamin D_3 (or plant-based vitamin D_2 or ergocalciferol). The product of this step, 25-hydroxyvitamin D_3, is converted into the active form of vitamin D_3, 1α,25-dihydroxyvitamin D, in a reaction catalyzed by CYP27B1. This 1α-hydroxylation takes place primarily in the kidney.

[Figure 1 - Click to Enlarge]

Mechanisms of action

Most, if not all, actions of vitamin D are mediated through a nuclear transcription factor known as the vitamin D receptor (VDR) (**Figure 2**) (5). Upon entering the nucleus of a cell, 1α,25-dihydroxyvitamin D binds to the VDR and recruits another nuclear receptor known as retinoid X receptor (RXR). In the presence of 1α,25-dihydroxyvitamin D, the VDR/RXR complex binds small sequences of DNA known as vitamin D response elements (VDREs) and initiates a cascade of molecular interactions that modulate the transcription of specific genes. Thousands of VDREs have been identified throughout the genome, and VDR activation by 1α,25-dihydroxyvitamin D is thought to directly and/or indirectly regulate 100 to 1,250 genes (6).

Figure 2. Conversion to the Active Form of Vitamin D and VDR-mediated Gene Regulation



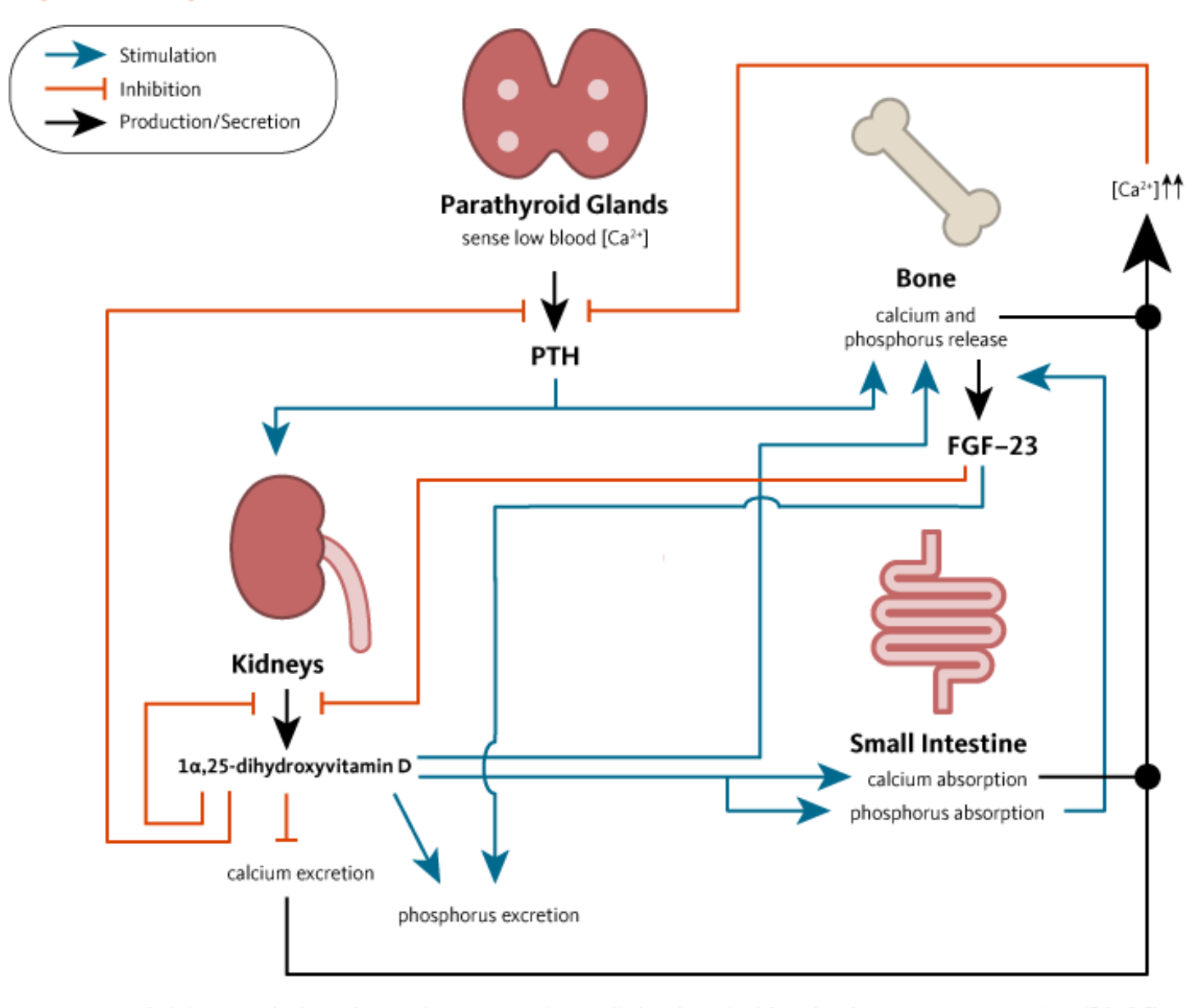
Mechanism of action. 25-Hydroxyvitamin D (25(OH)D) is the main form of vitamin D in the circulation. Most 25(OH)D and 1α,25-dihydroxyvitamin D ($1,25(OH)_2D$) molecules are transported bound to the vitamin D-binding protein and they enter cells via the megalin/tubulin complex. In kidney cells, 1α-hydroxylase (CYP27B1) catalyzes the conversion of 25(OH)D into $1,25(OH)_2D$. Parathyroid hormone (PTH), estradiol, and low phosphorus concentration ([P]) stimulate this reaction, whereas $1,25(OH)_2D$, fibroblast growth factor-23 (FGF-23), and high calcium concentration ([Ca]) inhibit it. $1,25(OH)_2D$ enters the circulation and is transported to extra-renal target tissues where it can regulate gene expression. In the nucleus of target cells, $1,25(OH)_2D$ binds to the vitamin D receptor (VDR), which heterodimerizes with the retinoid X receptor (RXR). VDR-RXR binds to vitamin D response elements (VDRE) in the promoter of vitamin D target genes. *25(OH)D, 25-hydroxyvitamin D; $1,25(OH)_2D$, 1α,25-dihydroxyvitamin D; [Ca], calcium concentration; CYP2R1, 1α-hydroxylase; DBP, vitamin D-binding protein; FGF-23, fibroblast growth factor-23; PTH, parathyroid hormone; [P], phosphorus concentration; RNA Pol II, RNA polymerase II; RXR, retinoid X receptor; VDR, vitamin D nuclear receptor; VDRE, vitamin D response element.*

[Figure 2 - Click to Enlarge]

Calcium balance

Maintenance of serum calcium concentrations within a narrow range is vital for normal functioning of the nervous system, as well as for bone growth and maintenance of bone density. Vitamin D is essential for the efficient utilization of calcium by the body (1). The parathyroid glands sense serum calcium concentrations and secrete parathyroid hormone (PTH) if calcium concentrations decrease below normal (**Figure 3**). Elevations in PTH stimulate the activity of the 25-hydroxyvitamin D_3-1α-hydroxylase enzyme in the kidney, resulting in the increased production of 1α,25-dihydroxyvitamin D. The active vitamin D form, 1α,25-dihydroxyvitamin D, is released into the circulation and transported to target tissues. Within target cells, 1α,25-dihydroxyvitamin D binds to and induces the activation of VDR, which leads to changes in gene expression that normalize serum calcium by (1) increasing the intestinal absorption of dietary calcium, (2) increasing the reabsorption of calcium filtered by the kidneys, and (3) mobilizing calcium from bone when there is insufficient dietary calcium to maintain normal serum calcium concentrations (7).

Figure 3. Regulation of Calcium and Phosphorus Homeostasis



Calcium and phosphorus homeostasis. A slight drop in blood calcium concentration ($[Ca^{2+}]$) results in the secretion of parathyroid hormone (PTH) by the parathyroid glands. PTH simulates the activity of CYP27B1 (25-hydroxyvitamin D-1α-hydroxylase enzyme) that catalyzes the hydroxylation of 25-hydroxyvitamin D into 1α,25-dihydroxyvitamin D. This active form of vitamin D (i) increases the reabsorption of calcium filtered by the kidneys and stimulates phosphorus excretion, (ii) increases the intestinal absorption of both calcium and phosphorus, and (iii) mobilizes calcium (and phosphorus) from bone when dietary calcium intake is insufficient. PTH also stimulates bone resorption that releases calcium and phosphorus. 1α,25-dihydroxyvitamin D inhibits its own production, as well as PTH synthesis, via negative feedback loops. FGF-23 is secreted by bone-forming cells (osteoblasts) in response to an increase in phosphorus intake. FGF-23 inhibits the synthesis of 1α,25-dihydroxyvitamin D and promotes phosphorus excretion in the urine.

$[Ca^{2+}]$, calcium concentration; FGF-23, fibroblast growth factor-23; PTH, parathyroid hormone.

[Figure 3 - Click to Enlarge]

Phosphorus balance

The regulations of calcium and phosphorus homeostasis are closely related, and the calciotropic hormones, PTH and 1α,25-dihydroxyvitamin D, can also control serum phosphorus. Specifically, 1α,25-dihydroxyvitamin D increases intestinal phosphorus absorption by stimulating the expression of a sodium-phosphate cotransporter in the small intestine. While PTH increases urinary excretion of phosphorus by reducing reabsorption in the kidney, it is not yet clear whether 1α,25-dihydroxyvitamin D can directly regulate renal phosphorus transport. The phosphaturic hormone fibroblast growth factor-23 (FGF-23), secreted by osteoblasts (bone-forming cells), limits the production of 1α,25-dihydroxyvitamin D by inhibiting 25-hydroxyvitamin D-1α-hydroxylase (**Figure 3**) (reviewed in 8).

Cell differentiation

Cells that are dividing rapidly are said to be proliferating. Differentiation results in the specialization of cells for specific functions. In general, differentiation of cells leads to a decrease in proliferation. While cellular proliferation is essential for growth and wound healing, uncontrolled proliferation of cells with certain mutations may lead to cancer. The active form of vitamin D, 1α,25-dihydroxyvitamin D, inhibits proliferation and stimulates the differentiation of cells through binding to the VDR (1).

Immunity

Acting through the VDR, 1α,25-dihydroxyvitamin D is a potent immune system modulator. The VDR is expressed by most cells of the immune system, including regulatory T cells and antigen-presenting cells, such as dendritic cells and macrophages (9). Under specific circumstances, monocytes, macrophages, and T cells can express the 25-hydroxyvitamin D_3-1α-hydroxylase enzyme and produce 1α,25-dihydroxyvitamin D, which acts locally to regulate the immune response (10, 11). There is considerable scientific evidence that 1α,25-dihydroxyvitamin D has a variety of effects on immune system function, which may enhance innate immunity and inhibit the development of autoimmunity (12). Conversely, vitamin D deficiency may compromise the integrity of the immune system and lead to inappropriate immune responses (see Autoimmune diseases).

Insulin secretion

The VDR is expressed by insulin-secreting cells of the pancreas, and the results of animal studies suggest that 1α,25-dihydroxyvitamin D plays a role in insulin secretion under conditions of increased insulin demand (13, 14). Cross-sectional and prospective studies suggest that insufficient vitamin D status may have an adverse effect on insulin secretion and glucose tolerance in type 2 diabetes mellitus (noninsulin-dependent diabetes mellitus) (reviewed in 15).

Blood pressure regulation

The renin-angiotensin system plays an important role in the regulation of blood pressure (16). Renin is an enzyme that catalyzes the cleavage (splitting) of a small peptide (angiotensin I) from a larger protein (angiotensinogen) produced in the liver. Angiotensin-converting enzyme (ACE) catalyzes the cleavage of angiotensin I to form angiotensin II, a peptide that can increase blood pressure by inducing the constriction of small arteries and by increasing sodium and water retention. The rate of angiotensin II synthesis is dependent on renin (17). Research in mice lacking the gene encoding the VDR indicates that 1α,25-dihydroxyvitamin D decreases the expression of the gene encoding renin through its interaction with the VDR (18). Since inappropriate activation of the renin-angiotensin system can contribute to the development of hypertension, achieving adequate vitamin D status may be important for decreasing the risk of high blood pressure (see Hypertension).

Deficiency

In vitamin D deficiency, calcium absorption cannot be increased enough to satisfy the body's calcium needs (4). Consequently, PTH production by the parathyroid glands is increased and calcium is mobilized from the skeleton to maintain normal serum calcium concentrations — a condition known as secondary hyperparathyroidism. Although it has long been known that severe vitamin D deficiency has serious consequences for bone health, research suggests that less obvious states of vitamin D deficiency are common and increase the risk of osteoporosis and various other health problems (see Disease Prevention).

Severe vitamin D deficiency

Rickets

In infants and children, severe vitamin D deficiency results in the failure of bone to mineralize. The process of mineralization, which involves the production of crystals of calcium phosphate by bone-forming cells, determines the hardness and strength of bones. Vitamin D deficiency severely affects rapidly growing bones. The growth plates of bones continue to enlarge, but in the absence of adequate mineralization, weight-bearing limbs (arms and legs) become bowed. In infants, rickets may result in delayed closure of the fontanels (soft spots) in the skull, and the rib cage may become deformed due to the pulling action of the diaphragm. In severe cases, low serum calcium concentrations (hypocalcemia) may cause seizures. Although fortification of food has led to complacency regarding vitamin D deficiency, nutritional rickets is still being reported throughout the world (19, 20).

Osteomalacia

Although adult bones are no longer growing, they are in a constant state of turnover, or "remodeling." In adults with severe vitamin D deficiency, the collagenous bone matrix is preserved, but bone mineral is progressively lost, resulting in a softening of bones (osteomalacia), bone pain, and increased risk of osteoporosis (21).

Muscle weakness and pain

Vitamin D deficiency causes muscle weakness and pain in children and adults. Muscle pain and weakness were prominent symptoms of vitamin D deficiency in a study of Arab and Danish Muslim women living in Denmark (22). In a cross-sectional study of 150 consecutive patients referred to a clinic in Minnesota for the evaluation of persistent, nonspecific musculoskeletal pain, 93% had serum 25-hydroxyvitamin D concentrations equal to or below 20 ng/mL, with a mean concentration of 12.1 ng/mL, which is indicative of vitamin D insufficiency (23). Loss of muscle strength greatly contributes to increased risk of falling and bone fractures, especially in older people (24). In addition, long-term vitamin D insufficiency may be a contributing factor to osteoporosis in the elderly (see Osteoporosis).

Risk factors for vitamin D deficiency

Both environmental factors and cultural practices result in variations in vitamin D status:

- Environmental conditions: Geographical locations, including latitude and altitudes, and atmospheric conditions (e.g., air pollution, presence of clouds) greatly influence the intensity of UVB radiation that reaches the ground. Seasonal changes also affect the quality and quantity of UVB rays and thus vitamin D production in skin (25-27).
- Concealed clothing style: In a study of 2,032 Middle Eastern women, who wore a headscarf or covered all skin for religious or cultural reasons, 96% had serum 25-hydroxyvitamin D concentrations less than 20 ng/mL, and 60% had vitamin D concentrations below 12 ng/mL (28). Rickets and osteomalacia are not uncommon in the Middle East and North African regions where children and women cover the majority or all of their skin whenever outside (29).
- Sun safety measures: Sun protection practices, including limiting sun exposure, wearing protective clothing and hats, and applying sunscreens, hinder skin exposure to sunlight and thus result in lower vitamin D_3 production and circulating vitamin D metabolites unless there is adequate oral intake. Of note, the application of sunscreen (2 mg/cm^2) with a sun protection factor (SPF) of 10 reduces UVB radiation by 90% (30).
- Exclusively breast-fed infants: Infants who are exclusively breast-fed and do not receive vitamin D supplementation are at high risk for vitamin D deficiency, particularly if they have dark skin and/or receive little sun exposure (19). Human milk generally provides 10 to 80 IU of vitamin D per liter (L), which corresponds to 0.2 to 1.5 g/day (8 to 60 IU/day) when using an average daily milk intake of 0.75 L (25 oz) (31). The American Academy of Pediatrics recommends that all breast-fed and partially breast-fed infants be given an oral vitamin D supplement of 400 IU/day (19). Maternal vitamin D supplementation during breast-feeding may contribute to improved vitamin D status of the breast-fed infant, especially in populations with a high prevalence of vitamin D deficiency (32). Older infants and toddlers exclusively fed milk substitutes (e.g., soy-based formulas) and weaning foods that are not vitamin D fortified are at risk for vitamin D deficiency (33).

The efficiency of vitamin D synthesis, absorption, and metabolism also depends on a variety of biological factors:

- Skin pigmentation: People with a dark complexion synthesize less vitamin D on exposure to sunlight than those with light-colored skin (34). A national US survey reported average serum 25-hydroxyvitamin D concentrations of 28.1 ng/mL, 21.6 ng/mL, and 16.9 ng/mL in Caucasian, Mexican American, and African American adults aged ≥20 years old, respectively (25).
- Genetic variations: An international, multicenter, genome-wide association study (GWAS) of 15 cohorts, including ~30,000 participants of European descent — known as the SUNLIGHT [Study of Underlying Genetic Determinants of Vitamin D and Highly Related Traits] consortium — identified common variations (called polymorphisms) in genes involved in cholesterol synthesis, hydroxylation, and vitamin D transport that influence vitamin D status (35). While genetic determinants of low vitamin D status are being identified in populations of European (36, 37) and Asian descent (38, 39), genome-wide association studies are needed in populations of African descent.
- Older age: The elderly have reduced capacity to synthesize vitamin D in skin when exposed to UVB radiation and are more likely to stay indoors or use sunscreen, which prevents vitamin D synthesis. It has been estimated that across Canada, the US, and Europe, the prevalence of vitamin D deficiency ranges between 20%-100% in free-living elderly (40). Moreover, institutionalized adults who are not supplemented with vitamin D are at extremely high risk of vitamin D deficiency (41, 42).
- Chronic kidney disease (CKD): Vitamin D deficiency in patients with impaired renal function is due to a reduced synthesis of 1α,25-dihydroxyvitamin D and an increased loss of 25-hydroxyvitamin D in urine (43).
- Fat malabsorption syndromes: Vitamin D deficiency is common among people with cystic fibrosis and both cholestatic and non-cholestatic liver diseases due to decreased absorption of dietary vitamin D and impaired conversion of vitamin D to 25-hydroxyvitamin D (reviewed in 44).
- Inflammatory bowel disease: People with inflammatory bowel disease like Crohn's disease appear to be at increased risk of vitamin D deficiency, especially those who have had small bowel resections (45).
- Obesity: Obesity (body mass index ≥30 kg/m^2) increases the risk of vitamin D deficiency (46). Once vitamin D is synthesized in the skin or ingested, it can be sequestered in body fat stores, making it less bioavailable to people with higher body fat mass. Moreover, vitamin D supplementation trials have shown that obese people reached much lower serum 25-hydroxyvitamin D concentrations compared to normal weight (BMI <25 kg/m^2) participants with equivalent oral dosages (47).
- Magnesium deficiency: Recent findings suggest that high magnesium intakes may reduce the risk of vitamin D insufficiency. Magnesium regulates the activity of critical enzymes in vitamin D metabolism, which would explain how magnesium deficiency negatively affects vitamin D status (48).

Assessing vitamin D nutritional status

Growing awareness that vitamin D insufficiency has serious health consequences beyond rickets and osteomalacia highlights the need for accurate assessment of vitamin D nutritional status. It is currently agreed that the measurement of total serum 25-hydroxyvitamin D concentration (1 ng/mL corresponding to 2.5 nmol/L) is the best indicator to evaluate vitamin D status. However, high-quality evidence is still needed to ensure that the current cutoff values are optimal to define states of insufficiency and deficiency (40). Moreover, only recently, efforts have been made toward the standardization of commercially and laboratory-developed 25-hydroxyvitamin D assays, such that guidelines have been developed using largely unstandardized research data (49). Although laboratory reference values for sufficient vitamin D status were initially based on serum 25-hydroxyvitamin D concentrations from cohorts of healthy individuals, additional studies have suggested that health-based cutoff values aimed at preventing secondary hyperparathyroidism and bone loss should be considerably higher. Indeed, while it is considered that serum 25-hydroxyvitamin D concentrations less than 8 to 10 ng/mL (20 to 25 nmol/L) indicate severe deficiency associated with rickets and osteomalacia, several studies have observed that PTH concentrations (50, 51) and calcium absorption (52) were not optimized with serum 25-hydroxyvitamin D concentrations below 32 ng/mL (80 nmol/L).

Yet, more recent studies have failed to find threshold values of serum 25-hydroxyvitamin D concentrations in relation to PTH suppression and optimal calcium absorption. On the one hand, a cross-sectional analysis of 312,962 clinical samples did not find any evidence of threshold for PTH suppression in the well-fitted curve displaying the inverse association between paired measurements of serum PTH and 25-hydroxyvitamin D, even with 25-hydroxyvitamin D concentrations beyond 70 ng/mL (175 nmol/L) (53). This contradicted an analysis of the US National Health and Nutrition Examination Survey (NHANES 2003-2006) that estimated maximum PTH suppression for 25-hydroxyvitamin D concentrations of 40 ng/mL (100 nmol/L) and above (54). In addition, both studies identified evidence of mild hyperparathyroidism (serum PTH >65 pg/mL) in individuals with serum 25-hydroxyvitamin D concentrations well beyond 20 ng/mL (50 nmol/L), questioning the use of serum PTH as a sensible indicator of vitamin D insufficiency (53, 54). On the other hand, a randomized, placebo-controlled trial in postmenopausal women with vitamin D insufficiency (serum 25-hydroxyvitamin D <20 ng/mL) supplemented with daily vitamin D_3 doses from 400 to 4,800 IU found little change (6%) in calcium absorption over a normal 25-hydroxyvitamin D concentration range of 20 to 66 ng/mL (55).

The current cutoffs proposed by the Institute of Medicine (IOM) are as follows: deficiency as serum 25-hydroxyvitamin D values <12 ng/mL (<30 nmol/L), insufficiency as serum 25-hydroxyvitamin D values of 12 to 19 ng/mL (30 to 49 nmol/L), and sufficiency as serum 25-hydroxyvitamin D values of 20 to 50 ng/mL (50 to 125 nmol/L) (56). The dietary reference intakes (EAR, RDA) set by the IOM are based on achieving circulating 25-hydroxyvitamin D concentrations (20 to 50 ng/mL) that are adequate to maintain bone health and optimal calcium absorption (57).

Yet, considering the potential role of circulating concentrations lower than 30 ng/mL in the burden of many chronic diseases (6), the US Endocrine Society has suggested to define cutoff values as follows: deficiency as serum 25-hydroxyvitamin D values ≤20 ng/mL (≤50 nmol/L), insufficiency as serum 25-hydroxyvitamin D values of 21 to 29 ng/mL (51 to 74 nmol/L), and sufficiency as serum 25-hydroxyvitamin D values of 30 to 100 ng/mL (75 to 250 nmol/L) (40). This alternate target range is supported by some observational studies, but it is not based on data from randomized controlled trials (see Disease Prevention) (47). With these latter cutoff values, studies from across the world have estimated that hypovitaminosis D is widespread and that children and adults of all ages are equally at risk of insufficiency and deficiency (58). Data from supplementation studies indicate that vitamin D intakes of at least 800 to 1,000 IU/day are required by adults living in temperate latitudes to achieve serum 25-hydroxyvitamin D concentrations of at least 30 ng/mL (75 nmol/L) (40).

Finally, total serum 25-hydroxyvitamin D concentrations may not always adequately reflect vitamin D bioavailability (59), and additional evidence is needed to improve the determination of vitamin D status in different ethnic populations.

The Recommended Dietary Allowance (RDA)

In 2010, the Food and Nutrition Board (FNB) of the IOM set a Recommended Dietary Allowance (RDA) based on the amount of vitamin D needed for bone health. While the RDA was increased from the adequate intake (AI) set in 1997, the optimal levels of recommended intakes and serum 25-hydroxyvitamin D to minimize hyperthyroidism and maximize bone health in the general population remain controversial (40). The RDA for vitamin D is listed in **Table 1** by life stage and gender.

Table 1. Recommended Dietary Allowance (RDA) for Vitamin D

Life Stage	Age	Males		Females	
		μg/day	IU/day	μg/day	IU/day
Infants (AI)	0-6 months	10	400	10	400
Infants (AI)	6-12 months	10	400	10	400
Children	1-3 years	15	600	15	600
Children	4-8 years	15	600	15	600
Children	9-13 years	15	600	15	600
Adolescents	14-18 years	15	600	15	600
Adults	19-70 years	15	600	15	600
Adults	71 years and older	20	800	20	800
Pregnancy	all ages	-	-	15	600
Breast-feeding	all ages	-	-	15	600

Disease Prevention

Mortality

In a nine-year follow-up analysis of the Third US National Health and Nutrition Examination Survey (NHANES III) that included 15,099 participants (of which 77% were Caucasians), serum concentrations of 25-hydroxyvitamin D — standardized as per the methodology developed by the Vitamin D Standardization Program [VDSP] — were examined in relation to mortality. The analysis suggested an increase in all-cause mortality with decreasing serum 25-hydroxyvitamin D concentrations <16 ng/mL (60). In contrast, the risk of all-cause mortality varied little for baseline serum 25-hydroxyvitamin D concentrations in the range of 16 to 40 ng/mL (60). Similar results were obtained in a meta-analysis of eight prospective cohort studies that considered the relationship between standardized 25-hydroxyvitamin D concentrations and mortality during a median follow-up period of 10.5 years. The risk of death was found to be 19% higher with 25-hydroxyvitamin D concentrations between 12 and 15.99 ng/mL and 56% higher with concentrations <12 ng/mL compared to the risk associated with concentrations between 30 and 39.99 ng/mL (61). A meta-analysis of 73 prospective cohort studies, including >800,000 participants, found that the lowest versus highest tertile of serum 25-hydroxyvitamin D concentrations was associated with greater risks of all-cause mortality (+35%), mortality due to cardiovascular disease (+35%), and mortality due to cancer (+14%) (62). Yet, a Mendelian randomization analysis — which limits bias due to confounding and reverse causation (63) — of data from three large Danish cohorts of 95,766 adults found a significant association of genetically low plasma 25-hydroxyvitamin D concentrations with all-cause and cancer-related mortality, but not with cardiovascular disease-related mortality (64). Finally, two meta-analyses of randomized controlled trials have suggested a modest reduction in all-cause mortality in older people supplemented with vitamin D and calcium, but not vitamin D alone (62, 65). Additional placebo-controlled trials need to examine further whether supplementation with vitamin D alone or in combination with calcium might help prevent premature death in replete individuals.

Osteoporosis

Vitamin D status, osteoporosis, and risk of fracture

Although the causes of osteoporosis are multifactorial, vitamin D insufficiency can be an important etiological factor in older adults. Osteoporosis affects one-third of women aged 60 to 70 years and two-thirds of women aged 80 years and above (66). A multinational (18 different countries with latitudes ranging from 64 degrees north to 38 degrees south) survey of more than 2,600 postmenopausal women with osteoporosis revealed that 31% of subjects had 25-hydroxyvitamin D concentrations <20 ng/mL (50 nmol/L) (67). In addition, a case-control study that included 111 hip fracture patients and 73 controls (median age, 83 years) found that lower serum concentrations of both 25-hydroxyvitamin D and vitamin K_1 in patients compared to controls were associated with an increased risk of hip fracture (68). Without sufficient vitamin D from sun exposure or dietary intake, intestinal calcium absorption can be significantly reduced. This increases PTH secretion by the parathyroid glands; sustained PTH elevation may result in increased bone resorption, which in turn may increase the risk of osteoporotic fracture (69).

Vitamin D supplementation and bone mineral density

The progressive loss of bone mineral density (BMD) leading to osteopenia (pre-osteoporosis) and osteoporosis is commonly observed in older adults, especially the elderly. The results of a meta-analysis of 23 randomized controlled trials with more than 4,000 participants (mean age, 59 years) showed little evidence for an effect of vitamin D supplementation on BMD at any of the five skeletal sites examined, including lumbar spine, femoral neck, trochanter, forearm, and total body. A significant increase in BMD was reported only at the femoral neck (70). It was, however, suggested that individuals in this age group would have adequate calcium intake and thus normal bone metabolism, explaining the lack of an effect of vitamin D in strengthening bone mass (71). Conversely, in older individuals, vitamin D supplementation is essential to correct and maintain adequate concentrations of serum 25-hydroxyvitamin D and to prevent secondary hyperparathyroidism and BMD loss (72).

Vitamin D supplementation and risk of fracture

A prospective cohort study that followed more than 72,000 postmenopausal women in the US for 18 years found that those who consumed at least 600 IU/day of vitamin D from diet and supplements had a 37% lower risk of osteoporotic hip fracture than women who consumed less than 140 IU/day of vitamin D (73). However, daily supplementation with 400 IU of vitamin D_3, in combination with 1,000 mg calcium, did not significantly reduce risk of hip fracture compared to a placebo in 36,282 postmenopausal women from the Women's Health Initiative trial (74), suggesting that there might be a threshold of vitamin D intake that is necessary to observe reductions in fracture risk. Results of a genetic analysis of data from this trial also suggested that beneficial effects of vitamin D and calcium supplementation on fracture risk might be limited to women with the lowest genetic risk of low BMD (75). Yet, this trial has been questioned for reasons that include poor adherence and the fact that participants were allowed to take additional vitamin D and calcium supplements that might have confounded the results. In addition, use of hormone replacement therapy was not considered in the study of the effect of vitamin D and calcium on skeletal health in postmenopausal women despite being a major confounding factor in this population (57, 76).

Another trial, the Randomised Evaluation of Calcium Or vitamin D (RECORD) study, reported that oral supplemental vitamin D_3 (800 IU/day) alone, or in combination with calcium (1,000 mg/day), did not prevent the occurrence of osteoporotic fractures in elderly adults who had already experienced a low-trauma, osteoporotic fracture (77). In this latter study as well, a number of limitations, including poor adherence and/or the fact that vitamin D supplementation did not raise serum 25-hydroxyvitamin D concentrations to a level that would protect against fractures, might explain the lack of an effect (78). Despite high adherence to treatment, the incidence of non-vertebral fracture was similar in postmenopausal women supplemented with vitamin D_3 (initial dose of 200,000 IU followed by 100,000/month) or placebo for over three years in the Vitamin D Assessment (ViDA) trial (79).

Nevertheless, the US Preventive Services Task Force that conducted the meta-analysis of 11 randomized, placebo-controlled trials, including 52,915 older people (of whom 69% were postmenopausal women), found that the supplementation of vitamin D (300-1,000 IU/day) and calcium (500-1,200 mg/day) for up to seven years resulted in a 12% reduction in the risk of any new fracture (80). Another meta-analysis of 11 randomized, double-blind, placebo-controlled trials on the effect of vitamin D supplementation in 31,022 individuals (91% women) 65 years and older indicated that those with the highest vitamin D intake (792-2,000 IU/day) had a 30% lower risk of hip fracture and a 14% lower risk of any non-spine fracture (81). Finally, a third meta-analysis of trials that examined the effect of combined vitamin D and calcium in preventing fractures in older men and postmenopausal women also concluded that the risk of new fractures, including hip fractures, was significantly reduced in those supplemented compared to controls (82). Interestingly, the three meta-analyses have found that the prevention of fractures by supplemental vitamin D and calcium was limited to institutionalized, older people. Indeed, the risk of fracture was not significantly reduced by vitamin D in community-dwelling seniors (80-82).

Vitamin D supplementation and postural balance, muscle strength, and risk of fall

A meta-analysis of seven observational studies in 840 fallers and 1,330 non-fallers found significantly lower serum 25-hydroxyvitamin D concentrations in fallers than in non-fallers (83). Moreover, another meta-analysis of four cohorts from three observational studies reported a modest yet significant inverse association between vitamin D status and the risk of fall (83). Several randomized controlled trials have examined the impact of vitamin D supplementation on muscle strength, postural balance, or risk of fall in older subjects. A meta-analysis of these trials found limited evidence of an effect of vitamin D supplementation on muscle strength and mobility, based on only one type of test for each outcome. Nevertheless, in a recent randomized, double-blind, placebo-controlled study in 160 postmenopausal women (ages, 50-65 years) with suboptimal vitamin D status (mean serum 25-hydroxyvitamin D concentration <20 ng/mL), supplementation with 1,000 IU/day of vitamin D_3 significantly improved vitamin D status, as well as upper and lower limb muscle strength and postural balance parameters (84, 85). The risks of fall and recurrent falls were found to be two- to three-fold greater in women in the control group than in those supplemented with vitamin D_3 (85). In contrast, another 12-month randomized controlled study in 200 older adults (of which 58% had a baseline serum 25-hydroxyvitamin D concentration <20 ng/mL) showed no benefits regarding lower extremity function or odds of falling in those supplemented with 2,000 IU/day (+/- 10 μg of calcidiol) compared to those who received 800 IU/day (86). The recently published post-hoc analysis of the ViDA trial found no differences in odds of falling and number of falls reported by 5,108 community-dwelling participants (ages, 50-84 years) regardless of whether they were randomized to receive supplemental vitamin D (100,000 IU/month, i.e. ~3,350 IU/day) or a placebo for a mean 3.4 years (79). Most ViDA participants had serum 25-hydroxyvitamin D concentrations ≥20 ng/mL, which might at least partly explain the lack of an effect of vitamin D on falls (87).

Overall, the current evidence suggests that vitamin D_3 supplements of 800-1,000 IU/day may be helpful in reducing falls and fracture rates in older adults. In order for vitamin D supplementation to be effective in preserving bone health, adequate dietary calcium (1,000 to 1,200 mg/day) should be consumed (see the article on Calcium) (88).

Cancer

Ecologic studies first suggested an association between Northern latitudes, vitamin D deficiency, and cancer incidence (89). Since the 1980s, several prospective cohort studies have examined the association of vitamin D intake or status and various types of cancer. A 2013 systematic review and meta-analysis of 16 prospective studies, including 137,567 subjects, reported an 11% reduction in total cancer incidence and a 17% reduction in cancer mortality with each 20 ng/mL (50 nmol/L) increase in circulating 25-hydroxyvitamin D concentrations. Yet, a sex-based subgroup analysis of eight studies found an inverse association between circulating vitamin D and cancer mortality in women, but not in men (90). In addition, increasing evidence suggests that a few variations in the gene coding for the vitamin D receptor (VDR) might influence individual vitamin D status and subsequently modify the susceptibility to site-specific cancers (91) and influence cancer survival (92). Finally, many malignant tumors have been found to express the VDR, including breast, lung, skin (melanoma), colon, and bone (93), suggesting that they might be susceptible to the effects of vitamin D. Numerous experimental studies have demonstrated that biologically active forms of vitamin D, such as 1α,25-dihydroxyvitamin D and its analogs, upon binding to the VDR, can control cell fate by inhibiting proliferation and/or inducing cell differentiation or death (apoptosis) of a number of cancerous cell types (94).

Colorectal cancer

The geographic distribution of colon cancer mortality resembles the historical geographic distribution of rickets (95), providing circumstantial evidence that decreased sunlight exposure and diminished vitamin D nutritional status may be related to an increased risk of colon cancer. Evidence from observational studies has largely supported this hypothesis. A recent meta-analysis of four prospective cohort studies, four cross-sectional studies, and seven case-control studies found an inverse relationship between circulating vitamin D and incidence of colorectal adenoma — a benign tumor that may transform to become malignant (96). The analysis identified a 32% risk reduction between top versus bottom quantiles of serum 25-hydroxyvitamin D concentrations (96). Additionally, there is strong evidence from meta-analyses of prospective cohort studies to suggest that higher vitamin D intakes and serum 25-hydroxyvitamin D concentrations are associated with reductions in colorectal cancer risk (97-99). The most recent meta-analysis of four prospective cohort, 17 nested case-control, and three case-control studies found a 38% reduced risk of colorectal cancer with high versus low quantiles of circulating 25-hydroxyvitamin D concentrations (100). A dose-response analysis estimated that serum 25-hydroxyvitamin D concentrations of ~20 to 30 ng/mL (compared to ≤12 ng/mL) were associated with a 17% lower risk of colorectal cancer, and the risk was even lower (-35%) with a serum concentration of 55 ng/mL (100). An earlier dose-response analysis based on five nested case-control studies had estimated that serum 25-hydroxyvitamin D concentrations ≥33 ng/mL (compared to ≤12 ng/mL) were associated with a 50% lower risk of colorectal cancer (101).

However, in a seven-year, randomized, double-blind, placebo-controlled trial in 36,282 postmenopausal women participating in the Women's Health Initiative study, a combination of supplemental vitamin D_3 (400 IU/day) and calcium (1,000 mg/day) did not lower incidence of colorectal cancer (102). Another randomized controlled trial of vitamin D_3 supplementation (1,000 IU/day), with or without calcium supplementation (1,200 mg/day), found no reduction in the risk of colorectal adenoma recurrence over a three-to-five year period, compared to placebo, after initial adenoma removal in participants (103). Whether these daily vitamin D doses are too low to detect any effect on cancer incidence is not clear (101, 104). Additional randomized clinical trials are needed to assess whether vitamin D supplementation could help prevent colorectal cancer. Moreover, it is uncertain whether genetic variations (polymorphisms) in the sequence of genes involved in vitamin D metabolism and function can influence the relationship between vitamin D status and risk of colorectal adenoma or colorectal cancer (105-107).

Finally, growing evidence suggests that adequate vitamin D status may be linked to better survival of colorectal cancer patients. A meta-analysis of five prospective studies found a 35% reduced risk of colorectal cancer-specific mortality in cancer patients with higher serum 25-hydroxyvitamin D concentrations. A dose-response analysis estimated that every 8 ng/mL increase in 25-hydroxyvitamin D concentration was associated with a 10% decrease in colorectal cancer mortality (108).

Breast cancer

Although ecologic evidence suggests that breast cancer mortality rises with increasing latitudes and decreasing sunlight exposure (109), the most current observational data provide little support for an association between vitamin D nutritional status and risk of breast cancer. An early prospective study of women who participated in the First US National Health and Nutrition Examination Survey (NHANES I) found that Caucasian women with adequate sunlight exposure and dietary vitamin D intake had a significantly reduced risk of breast cancer 20

Nutrition Examination Survey (NHANES I) found that Caucasian women with adequate sunlight exposure and dietary vitamin D intake had a significantly reduced risk of breast cancer 20 years later (110). Nonetheless, when this study was included in a meta-analysis with nine more recent prospective studies, there was no significant difference in the risk of developing breast cancer between the highest and lowest levels of vitamin D intakes (111). Moreover, whether an association exists between circulating vitamin D concentrations and risk of breast cancer is unclear. One meta-analysis of 14 observational studies (9,110 cases and 16,244 controls) reported an overall risk reduction of 16% when the highest quantile of serum 25-hydroxyvitamin D concentrations was compared to the lowest. This inverse association was statistically significant in postmenopausal women but not in premenopausal women (112). Yet, another meta-analysis that included a similar set of 14 prospective studies (two studies were different) found no overall association (111). Additionally, a meta-analysis of studies conducted in patients in the early stage of breast cancer identified associations between inadequate vitamin D status and increased risks of recurrence and death (113). Evidence from randomized controlled trials is currently too limited to conclude whether vitamin D supplementation may reduce breast cancer incidence (reviewed in 114).

Nonetheless, three meta-analyses have found an inverse association between circulating vitamin D concentrations and breast cancer-related mortality (111, 115, 116). In one meta-analysis of one retrospective and five prospective cohort studies, the highest versus lowest categories of serum vitamin D concentrations was associated with a 33% reduction in mortality; a dose-response analysis found a 12% reduction per 8 ng/mL increase in serum vitamin D (115).

Finally, current evidence does not suggest that specific genetic variations in the gene coding for the VDR may influence the risk of breast cancer (117, 118).

Other types of cancer

Evidence associating vitamin D status with other types of cancer is currently limited. While incidence of prostate cancer appears to be inversely associated with the availability of sunlight, prospective cohort studies have not generally found significant relationships between serum 25-hydroxyvitamin D concentrations and subsequent risk of developing prostate cancer (119, 120). In fact, some studies have suggested an increased risk of prostate cancer with higher circulating vitamin D concentrations. For example, a nested case-control study of men (622 cases and 1,451 controls) from Scandinavia found a U-shaped relationship between serum 25-hydroxyvitamin D concentrations and prostate cancer risk. In that study, serum 25-hydroxyvitamin D concentrations of 7.6 ng/mL or lower, or 32 ng/mL or higher, were associated with increased prostate cancer risk (121). A meta-analysis of 17 nested case-control studies, three prospective cohort studies, and one retrospective cohort study found a 17% increased risk of prostate cancer in individuals in the highest versus lowest categories of blood 25-hydroxyvitamin D concentrations (122). Potential confounding factors that might explain the detection of a slight increase in prostate cancer cases in men with high circulating vitamin D concentrations have been highlighted in a recent publication (123).

Finally, recent meta-analyses of observational studies found an inverse relationship between vitamin D status and risk of lung cancer (124, 125) and bladder cancer (126, 127). Yet, in the few and often heterogeneous studies published to date, serum 25-hydroxyvitamin D concentrations were not associated with other cancer types, including non-Hodgkin's lymphoma (128), ovarian cancer (129), gastric cancer (130), or skin cancers (131).

Autoimmune diseases

Insulin-dependent diabetes mellitus (type 1 diabetes mellitus), multiple sclerosis (MS), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) are examples of autoimmune diseases. Autoimmune diseases occur when the body mounts an immune response against its own tissue, rather than a foreign pathogen. In type 1 diabetes mellitus, insulin-producing β-cells of the pancreas are the target of an inappropriate immune response. In MS, the targets are the myelin-producing cells of the central nervous system, and in RA, the targets are the collagen-producing cells of the joints (132). SLE is characterized by the presence of a large spectrum of autoantibodies resulting in potential damage to multiple tissues (133). Autoimmune responses are mediated by immune cells called T cells. The biologically active form of vitamin D, 1α,25-dihydroxyvitamin D, has been found to modulate T cell responses, such that the autoimmune responses are diminished. Ecologic studies have found that the prevalence of autoimmune diseases (particularly for MS; 134) increases as latitude increases, suggesting that lower exposure to UVB radiation and associated decreases in skin vitamin D synthesis may play a role in the pathology of these diseases. Results of several prospective cohort studies also suggest that adequate vitamin D status at different ages (including *in utero*, early childhood, and during adolescence) could possibly decrease the risk of autoimmune diseases.

Type 1 diabetes mellitus

Lower levels of circulating vitamin D have been reported in patients newly diagnosed with type 1 diabetes mellitus compared to age- and sex-matched non-diabetic subjects (135, 136). A greater prevalence of vitamin D insufficiency and deficiency has also been observed in prediabetic children who developed multiple islet autoantibodies (antibodies against insulin-secreting pancreatic cells) compared to autoantibody-negative children. However, a prospective study that followed the cohort of prediabetic children found that their vitamin D status, defined as either insufficient, deficient, or sufficient, was not associated with rate of progression to type 1 diabetes after 5 or 10 years of follow up (137). An earlier prospective cohort study of children born in Finland during the year 1966 and followed for 30 years found that children supplemented with vitamin D during the first year of life had an 88% lower risk of developing type 1 diabetes compared to those receiving no supplementation. Moreover, children suspected of having had rickets (severe vitamin D deficiency) during the first year of life showed a significantly higher risk of developing type 1 diabetes (138). Thus, vitamin D supplementation appears protective against type 1 diabetes onset, and suboptimal vitamin D status in infancy may have long-term effects on immune responses later in life.

There are also limited data suggesting that maternal vitamin D insufficiency during pregnancy may influence the risk of type 1 diabetes in offspring. In a recent case-control study, the risk of childhood onset of type 1 diabetes was more than two-fold greater in children whose mothers had serum 25-hydroxyvitamin D concentrations <21.6 ng/mL (54 nmol/L) during the last trimester of pregnancy compared to children born from women with serum 25-hydroxyvitamin D >35.6 ng/mL (89 nmol/L) (139). Other case-control studies have found that vitamin D supplementation during pregnancy was associated with a lower risk of their children developing diabetes-related autoantibodies (140, 141). However, a larger study conducted in mothers of children at increased genetic risk for diabetes reported no association between the appearance of islet autoantibodies and/or diabetes onset in offspring in the first year of life and maternal vitamin D intake during pregnancy (142). Another case-control study failed to observe a relationship between serum 25-dihydroxyvitamin D during early pregnancy and type 1 diabetes diagnosis in offspring (143). Large prospective studies are needed to establish whether maternal vitamin D status during pregnancy can influence the risk of type 1 diabetes in offspring.

Finally, the relationship of polymorphisms in vitamin D metabolism-related genes and type 1 diabetes is currently under investigation. It has been proposed that specific polymorphisms in genes, such as *CYP27B1* (coding for 25-hydroxyvitamin D$_3$-1α-hydroxylase) and *VDR*, may be functionally relevant to the action of vitamin D and may thus affect disease susceptibility. In a study conducted in 8,517 children and adolescents with type 1 diabetes and 7,320 control subjects, polymorphisms in genes involved in cholesterol synthesis and vitamin D hydroxylation were linked to circulating vitamin D concentrations and diabetic status (26).

Multiple sclerosis

Low levels of sun exposure and vitamin D deficiency appear to be associated with the development of multiple sclerosis (MS). Poor vitamin D status may compromise the function of specific immune cells critical in the regulation of various immune responses and help trigger autoimmunity in MS (144). Genetic determinants of low vitamin D status have been recently linked to an increased susceptibility to adult-onset MS in a Mendelian randomization analysis of data from the Multiple Sclerosis Genetics Consortium (145). This echoed the results of several observational studies that suggested an association between vitamin D sufficiency and decreased MS risk. A retrospective study of levels of ambient UV radiation and cases of MS conducted in Australia revealed that MS incidence in offspring was inversely correlated to maternal exposure to UV during early pregnancy (146). Sun exposure was also used as a surrogate marker for vitamin D exposure in a recent case-control study that included 1,660 MS patients and 3,050 controls. The authors found that infrequent outdoor activities and the use of sunscreen during early childhood and adolescence were associated with an increased risk of developing MS later in life (147). In a cross-sectional study, sun exposure and intake of cod liver oil (rich in vitamin D) during childhood were linked to later symptom onset among veterans with relapsing MS (148). Additionally, a case-control study in US military personnel, including 257 cases of diagnosed MS, found that Caucasian subjects in the highest quintile of serum 25-hydroxyvitamin D (>39.6 ng/mL) had a 62% lower risk of developing MS compared to the lowest quintile (<25.3 ng/mL) (149). Further, in two large cohorts of over 187,000 US women followed for at least 10 years, vitamin D supplement use (≥400 IU/day) was associated with a 41% reduction in the risk of developing MS (150). Another prospective, uncontrolled study monitored incidence of relapse in relation to vitamin D status in 156 patients with relapsing-remitting MS before and after they were given supplemental vitamin D (100,000 IU/month; 6-42 months, median of 31 months), in addition to first-line immunomodulatory therapy (151). Each 4 ng/mL increase in serum 25-hydroxyvitamin D concentration was associated with a 14.9% decrease in incidence of relapse (151). In a multicenter study conducted in patients newly diagnosed with a clinically isolated syndrome (CIS) and treated with interferon (IFN)-β, vitamin D status was predictive of MS disease activity and progression. Higher serum 25-hydroxyvitamin D concentrations (≥20 ng/mL or ≥50 nmol/L) in the first year following CIS diagnosis predicted a longer time to MS diagnosis, lower number of new lesions, and lower changes in lesion and brain volume during the subsequent four years of follow-up (152). However, a retrospective study suggested that vitamin D status in patients with relapsing-remitting MS had no predictive value regarding the time to conversion to secondary progressive MS, which is characterized by a worsening of disability (153).

Clinical trials have failed to demonstrate any benefit of vitamin D supplementation, alone or in combination with IFN-β treatment, with respect to relapse rates and disability-related symptoms in MS patients (154, 155). In other trials, supplemental vitamin D$_3$ also failed to demonstrate immunomodulary activities (156-159). In a recent randomized, placebo-controlled trial in 53 IFN-β-treated patients with relapsing-remitting MS, supplementation with vitamin D$_3$ (7,000 IU/day for four weeks, followed by 14,000 IU/day until week 48) showed little effect on the proportion of some regulatory T and B lymphocytes over the 48-week study period. Vitamin D$_3$ only appeared to help maintain the proportion of anti-inflammatory $CD4^+$ T cells — which decreased in patients given placebo — but failed to enhance their reactivity when stimulated with 1,25-dihydroxyvitamin D *in vitro* (157). In another trial, supplementation with vitamin D$_3$ (10,400 IU/day for three months) to patients with relapsing-remitting MS was found to reduce the proportion of pro-inflammatory IL-17-producing $CD4^+$ T cells, which are thought to play a central role in MS development (160).

Rheumatoid arthritis

Vitamin D deficiency may also be implicated in the etiology and/or progression of rheumatoid arthritis (RA), although evidence is mainly from animal studies. The absence of vitamin D receptors (VDR) in genetically modified mice has been linked to higher levels of inflammation and increased susceptibility to autoimmunity (161). When transgenic mice that spontaneously develop inflammatory arthritis are also deficient in VDR, they develop a more aggressive form of chronic arthritis (162). Also, specific polymorphisms in the *VDR* gene have been linked to an increased susceptibility to RA in certain populations, although how these genetic variants influence vitamin D functionality is not fully understood (163-165). The current data, however, point to a role for vitamin D in modulating the inflammatory process that underlies many chronic diseases, including RA. Several cross-sectional studies in individuals with moderate-to-high levels of inflammation have reported either no association or an inverse association between circulating 25-hydroxyvitamin D concentration and markers of inflammation. Nonetheless, there is a lack of intervention trials to show whether vitamin D supplementation could limit inflammation and reduce disease risk (including RA) in subjects with high inflammation levels (166).

At this time, it remains unclear whether the prevalence of vitamin D deficiency is linked to RA incidence. In a large cohort study of nearly 30,000 postmenopausal US women, subjects with the highest total vitamin D intakes (≥467.7 IU/day) had a 33% lower risk of developing RA after 11 years of follow-up than those with the lowest intakes (<221.4 IU/day) (167). Yet, more recent analyses of two large cohorts of nearly 200,000 US women followed for several decades found no association between reported vitamin D dietary intakes (using food frequency questionnaires) during adolescence or adulthood and incidence of RA later in life (168, 169). Moreover, several studies that explored the relationship between circulating vitamin D and disease activity in RA patients have reported mixed results (reviewed in 170). Yet, two recent meta-analyses of observational studies found an inverse relationship between vitamin D status and disease activity in RA patients, assessed using the Disease Activity Score 28 (DAS28) (171, 172). Finally, there is a dearth of studies exploring the effect of vitamin D supplementation on disease activity in arthritis subjects. A small randomized, double-blind, placebo-controlled study in 22 RA patients failed to demonstrate improvements in disease activity and inflammation level in subjects supplemented with calcium (1,500 mg/day) and high doses of vitamin D$_2$ (ergocalciferol; averaging over 4,500 IU/day) for a year compared to placebo (173). Another three-month, randomized controlled trial in 41 women with early RA found no additional benefits of supplemental vitamin D$_3$ (one bolus dose of 300,000 IU) to standard care (methotrexate and glucocorticoids) regarding T-helper lymphocyte enumeration, cytokine production, or clinical parameters including disease activity (174). Supplemental vitamin D also failed to reduce disease recurrence rate in RA patients enrolled in two small randomized controlled trials (175, 176). Since these studies have several limitations, including small sample size, additional research is warranted.

Systemic lupus erythematosus

More prevalent and severe in non-Caucasian populations (Hispanics, African descendants, and Asians) (177), systemic lupus erythematosus (SLE) is an autoimmune disease with heterogeneous clinical manifestations. The disease can potentially affect most tissues and organs, including skin (skin rash and photosensitivity), kidneys (nephritis), and joints (arthritis). There is evidence of a role for vitamin D in the prevention of SLE in animal models (178). Interestingly, a recent meta-analysis of 11 case-control studies found that specific *VDR* polymorphisms were linked to SLE in Asians particularly (179). However, the functional relevance of such genetic variants is not known (180). Analyses of two large prospective cohort studies of nearly 200,000 US women failed to show an association between dietary vitamin D intake (measured by food frequency questionnaire) during adolescence or adulthood and incidence of SLE later in life (168, 169).

Yet, a suboptimal vitamin D status is commonly observed in subjects with SLE, and this is partly explained by the lack of sunlight exposure, which tends to aggravate disease symptoms (181, 182). Serum concentrations of 25-hydroxyvitamin D were inversely correlated with measures of disease activity in a cohort of 378 patients with SLE (183). The correction of vitamin D insufficiency with high levels of vitamin D$_3$ (100,000 IU/week for one month followed by 100,000 IU/month for six months) in 20 subjects with SLE was linked to a reduction in signs of immune imbalance and in levels of autoantibodies typically detected in SLE, suggesting a therapeutic value for vitamin D in disease treatment (184). Another prospective study conducted in 52 vitamin D-deficient patients with cutaneous lupus erythematosus (a type of lupus with skin disorders only) reported a reduction in disease severity in the group supplemented with vitamin D$_3$ (1,400 IU/day initially, followed by 800 IU/day) and calcium for one year compared to untreated patients (185). Supplementation with vitamin D$_3$ (200 IU/day for one year) was also able to reduce the level of inflammatory cytokines in a randomized, placebo-controlled study conducted in 267 patients with SLE (186). In another randomized, placebo-controlled trial, supplementation with vitamin D$_3$ (50,000 IU/week for six months) improved SLE disease activity index (SLEDAI) and European Consensus Lupus Activity Measurement (ECLAM) scores, as well as some measures of fatigue in young adults with juvenile-onset SLE (187). However, in two other recent studies, supplementation with vitamin D$_3$ (weekly/monthly bolus doses equivalent to ~800 to 7,000 IU/day for 6 to 24 months) improved vitamin D status in SLE patients but failed to show any benefit regarding disease activity (188, 189). While oral vitamin D administration to SLE patients is well tolerated, its efficacy remains questionable and deserves further investigation in clinical trials.

Summary

Thus, evidence from human epidemiological studies suggests that while it cannot yet be concluded that vitamin D supplementation is beneficial in prevention or treatment of autoimmune disease, it is reasonable to assume that correcting vitamin D insufficiency and maintaining sufficient levels could possibly help decrease disease risk (190).

Cardiovascular disease

Hypertension (high blood pressure)

Hypertension is a well-known risk factor for cardiovascular disease (CVD) (191). The results of observational and clinical studies suggest a role for vitamin D in lowering blood pressure, which may be partly explained by the fact that 1α,25-dihydroxyvitamin D inhibits renin synthesis (see Function). Thus, vitamin D deficiency and subsequent upregulation of the renin-angiotensin system may contribute to high blood pressure and CVD risk. It has also been suggested that elevated PTH concentrations may increase the risk of hypertension and CVD (6). Yet, in a recent prospective cohort study of 3,002 individuals (mean age, 59 years at baseline), the incidence of hypertension, which affected 41% of participants during the nine year follow-up period, was not higher in those with serum 25-hydroxyvitamin D concentrations lower than 20 ng/mL and was only marginally associated with elevated PTH concentrations (192). Nevertheless, a meta-analysis of seven prospective studies, including a total of 48,633 participants with nearly 5,000 incident hypertension cases, found a 30% lower risk of hypertension in those in the top versus bottom tertiles of serum 25-hydroxyvitamin D concentrations. The dose-response analysis estimated that every 10 ng/mL increase in serum 25-hydroxyvitamin D concentration was associated with a 12% lower risk of hypertension (193). Another meta-analysis of four prospective and 14 cross-sectional studies also reported an inverse relationship between circulating 25-hydroxyvitamin D and hypertension (194).

Endothelial dysfunction

Vascular endothelium dysfunction, which contributes to an increased risk of cardiovascular disease (CVD), is common in patients with chronic kidney disease (CKD) (195). In CKD patients, abnormal endothelial function is associated with low values of flow-mediated dilation (FMD) of the brachial artery, a surrogate marker of vascular health. In a recent study conducted in subjects with mild-to-moderate CKD, serum 25-hydroxyvitamin D concentrations were positively associated with FMD values, suggesting a link between suboptimal vitamin D status and endothelial dysfunction (196). In a preliminary intervention study, 26 patients with moderate CKD and vitamin D insufficiency (mean value, 17.2 ng/mL) were supplemented twice with 300,000 IU of vitamin D$_3$ (at weeks 1 and 8) and followed for a total of 16 weeks. Vitamin D supplementation nearly doubled serum 25-hydroxyvitamin D concentrations and decreased PTH concentrations by 68.5%; improved vitamin D status was accompanied by increased FMD values and reduced levels of endothelial dysfunction markers (197). A recent meta-analysis of 12 small randomized controlled trials in participants at high risk for CVD found a significant increase in FMD with vitamin D supplementation (daily doses, 2,500-5,000 IU; weekly dose, 50,000 IU; monthly dose, 60,000 IU; single-bolus doses, 100,000-200,000 IU) for eight weeks to six months (198).

Cardiovascular events in observational studies and clinical trials

To date, the many epidemiological studies investigating the relationship between vitamin D and outcomes of CVD have provided mixed results (reviewed in 199). Recent Mendelian randomization studies found no association between genetically low serum 25-hydroxyvitamin D concentrations and risks of coronary heart disease, ischemic heart disease, or myocardial infarction (200, 201), suggesting that associations reported in observational studies may be due to confounding or reverse causation. In the RECORD trial in 5,292 older people (see Osteoporosis), supplementation with 800 IU/day of vitamin D$_3$ (± calcium) reduced the risk of first cardiac failure but had no effect on the risk of myocardial infarction and stroke compared to supplementation with calcium alone or placebo (202). Data on the effect of vitamin D supplementation on cardiovascular events were collected from 21 randomized controlled studies (including the RECORD trial) in 13,033 participants (≥60 years old) and combined in a meta-analysis (202). No effect of vitamin D (including vitamin D analogs) was found for major cardiovascular events, including heart failure, myocardial infarction, and stroke over follow-up periods of 1 to 6.2 years (202). However, caution is advised when interpreting these results since the trials were initially designed to evaluate the effect of vitamin D on bone health, and cardiovascular outcomes were not primary endpoints. Several randomized controlled trials exploring the effect of vitamin D supplementation on CVD risk are currently underway (203), including two large trials, the Vitamin D and Omega-3 Trial (VITAL) in the US (204) and the D-Health trial in Australia (205). The results of one randomized controlled trial, the Vitamin D Assessment (ViDA) trial in New Zealand, were recently published. The total number of CVD events and time to first CVD event during follow-up did not differ between those supplemented with vitamin D$_3$ (initial dose of 200,000 IU for the first month followed by monthly doses of 100,000 IU) and those given a placebo for a median 3.3 years (206).

Type 2 diabetes mellitus

People with metabolic syndrome are at increased risk for type 2 diabetes mellitus (noninsulin-dependent diabetes mellitus) and cardiovascular disease (CVD). Metabolic syndrome refers to several metabolic disorders, including dyslipidemia, hypertension, insulin resistance, and obesity. A recent study found that the prevalence of type 2 diabetes was associated with low levels of serum 25-hydroxyvitamin D (<30 ng/mL) in 1,801 patients with metabolic syndrome. During an eight-year follow-up period, lower risks of all-cause mortality (72% lower risk) and CVD-specific mortality (64% lower risk) were reported in individuals with serum 25-hydroxyvitamin D concentrations over 30 ng/mL (75 nmol/L) when compared to those with concentrations below 10 ng/mL (25 nmol/L) (207).

In healthy people, vitamin D sufficiency is positively correlated with insulin sensitivity and adequate pancreatic β-cell function. Conversely, vitamin D deficiency might affect glucose homeostasis and cause impaired glucose tolerance and insulin resistance (208). In a cross-sectional study conducted in 12,719 adults, of whom 4,057 had prediabetes (i.e., an increased risk of developing type 2 diabetes), the prevalence of prediabetes was associated with lower concentrations of serum 25-hydroxyvitamin D (≤32.4 ng/mL). Subjects with the lowest concentrations of serum 25-hydroxyvitamin D (≤17.7 ng/mL) were more likely to be current smokers, obese, and have hypertension (209). Vitamin D insufficiency in high-risk individuals may accelerate the progression to overt diabetes. In a prospective study of 2,378 middle-aged men and women followed for 8 to 10 years, the risk for progression to type 2 diabetes from prediabetes was 62% lower in women and 60% lower in men in the highest compared to the lowest quartile of circulating vitamin D (>28.4 ng/mL vs. <18.5 ng/mL). A dose-response analysis measured an average 23% reduction in the risk of progression to type 2 diabetes for every 4 ng/mL (10 nmol/L) increment in serum 25-hydroxyvitamin D concentration (210). A recent review and meta-analysis of 18 prospective cohort studies, including over 210,000 participants followed for a median period of 10 years, found that individuals in the top third of vitamin D levels (reported as either circulating vitamin D or dietary intakes) had lower risks of developing type 2 diabetes (19% lower risk) and metabolic syndrome (14% lower risk) compared to those in the bottom third (211). In another meta-analysis of nine prospective studies, including 28,258 older people (mean age, 67.7 years), lower versus higher circulating vitamin D concentrations at baseline were found to be associated with a 17% higher risk of developing type 2 diabetes over a median follow-up period of 7.3 years (212). Currently, limited evidence suggests that vitamin D supplementation may improve insulin sensitivity in individuals with glucose intolerance or manifest type 2 diabetes (213-216). There is a need for well-designed clinical trials to examine whether maintaining adequate vitamin D levels can prevent adverse metabolic outcomes in healthy and at-risk individuals.

Neurodegenerative diseases

Cognitive impairment and Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia, characterized by the presence of extra-neuronal β-amyloid plaques and intra-neuronal Tau protein aggregates (known as neurofibrillary tangles) in the brain. Mechanistic models currently investigated in animal research suggest that vitamin D deficiency or disorders of vitamin D metabolism and/or the disruption of the vitamin D-VDR pathway in the cerebral regions of the cortex and hippocampus may be involved in the degeneration of neurons and loss of cognitive functions (217). Experimental evidence supporting a role for vitamin D in calcium channel regulation, neuroprotection, and immunomodulation in the central nervous system also implies that low vitamin D status may precede or contribute to cognitive dysfunction with age (218).

A number of observational studies have examined cognitive decline and degenerative brain disease in the elderly in relation to dietary intake of vitamin D and serum 25-hydroxyvitamin D concentration. In a large French cohort study on osteoporosis and hip fractures in postmenopausal women, impairments in global cognitive performance, assessed with the Pfeiffer Short Portable Mental State Questionnaire (SPMSQ), were associated with lower dietary intakes of vitamin D (<1,400 IU/week vs. ≥1,400 IU/week) in 5,596 elderly women (mean age, 80.5 years) (219). A seven-year follow-up study of a subgroup of 498 women indicated that the risk of Alzheimer's disease (but not other types of dementia) was 77% lower in those in the highest versus the lowest quintiles of vitamin D dietary intakes at baseline (220). Some, but not all, observational studies have found an association between low serum 25-hydroxyvitamin D concentrations and mild cognitive impairment in older adults (219, 221, 222). The cross-sectional and longitudinal analysis of two prospective studies, which included 1,604 men (223) and 6,257 women (224) aged 65 and over, reported a 60% greater odds of cognitive impairment at baseline and a 58% increased risk of cognitive decline during a four-year follow-up period in women, but not in men, with vitamin D deficiency (circulating 25-hydroxyvitamin D <10 ng/mL vs. ≥30 ng/mL). In the nested case-control, multiethnic, Singapore Kidney Eye Study, which included 2,273 individuals (mean age, 70.4 years), serum 25-hydroxyvitamin D concentrations were inversely correlated with cognitive deficits affecting retrograde episodic memory, semantic memory, and orientation in time, as assessed by the Abbreviated Mental Test (AMT) (225).

Yet, systematic reviews and meta-analyses of observational studies have given mixed results regarding the association of vitamin D status with cognitive performance and AD (226-230). Moreover, the recent analysis of data from 1,182 men followed for 18 years in the Uppsala Longitudinal Study of Adult Men (ULSAM) failed to find associations of genetic determinants of vitamin D synthesis, vitamin D intakes, and plasma 25-hydroxyvitamin D concentrations with risks of cognitive impairments, AD, vascular dementia, or all-cause dementia (231). In contrast, another Mendelian randomization study associated genetic determinants of low vitamin D status to higher risk of AD in the International Genomics of Alzheimer's Project dataset (17,008 AD cases and 37,154 healthy cases) (232).

Nevertheless, the prevalence of vitamin D insufficiency/deficiency ranges between 70% and 90% in older adults, and correcting low concentrations of serum 25-hydroxyvitamin D may help improve cognitive processes, in particular executive functions (233). In a small, non-randomized controlled study in an outpatient clinic, global cognitive function was assessed at baseline and after 16 months in 20 patients supplemented with 800 IU/day (or 100,000 IU/month) of vitamin D and in 24 control subjects. The supplementation of outpatients with vitamin D resulted in the correction of low vitamin D status (average serum 25-hydroxyvitamin D concentration was 16.8 ng/mL at baseline and 30 ng/mL at 16 months) and was associated with a significantly improved scoring in cognition tests compared to the non-supplemented group (234). In a small randomized, placebo-controlled clinical trial in 32 mild-to-moderate AD patients receiving nasal insulin, high doses of vitamin D$_2$ supplementation for eight weeks (up to 36,000 IU/day) did not significantly improve cognitive performance compared to low doses (1,000 IU/day) (235). More research is needed to investigate a causal relationship between vitamin D repletion and potential long-term cognitive benefits in older adults. Further, it is of great importance to evaluate whether correcting vitamin D deficiency in cognitively impaired subjects can improve the impact of anti-dementia therapy (236).

Parkinson's disease

Parkinson's disease (PD) has been associated with a high prevalence of vitamin D insufficiency among patients, especially those with greater mobility problems (237). A case-control study of 296 outpatients with a mean age of 65 years indicated that 23% of PD subjects had serum 25-hydroxyvitamin D concentrations lower than 20 ng/mL compared to 16% and 10% of AD and healthy individuals, respectively (238). In a prospective cohort study conducted among 3,173 men and women aged 50-79 years and free of PD at baseline, individuals in the highest quartile of serum 25-hydroxyvitamin D (≥20 ng/mL for women and ≥22.8 ng/mL for men) had a 67% lower risk of PD compared to those in the lowest quartile (≤10 ng/mL for women and ≤11.2 ng/mL for men) (239). Meta-analyses pooling data from observational studies all showed that vitamin D inadequacy was more likely reported in subjects with PD than in healthy controls (240-242).

In a randomized, double-blind, placebo-controlled study, 112 PD patients (mean age, 72 years) on standard PD treatment were supplemented with 1,200 IU/day of vitamin D or a placebo for 12 months. Vitamin D supplementation nearly doubled serum 25-hydroxyvitamin D concentration (from mean of 22.5 ng/mL to 41.7 ng/mL) in supplemented subjects and limited the progression of PD, as indicated by a greater proportion of patients who showed no worsening (as assessed by the Hoehn and Yahr stage and the United Parkinson Disease Rating Scale part II) in the supplemented group compared to the placebo group (243). It is not known whether vitamin D insufficiency has a role in the pathogenesis of the disease, but the repletion of vitamin D may provide health benefits that go beyond the prevention and/or the treatment of PD. For example, vitamin D deficiency may contribute to the increased risk of osteoporosis and bone fracture in individuals with neurologic disorders, including PD and multiple sclerosis (244-246). Interestingly, sunlight exposure was found to be associated with improved vitamin D status, higher bone mineral density of the second metacarpal bone, and lower incidence of hip fracture in a prospective study conducted in 324 elderly people with PD (247).

Adverse pregnancy outcomes

A systematic review and meta-analysis of 31 observational studies on maternal vitamin D status and pregnancy outcomes indicated that vitamin D insufficiency may be associated with gestational diabetes mellitus, preeclampsia, and bacterial vaginosis in pregnant women. Low maternal serum vitamin D during pregnancy was also linked to an increased risk for small-for-gestational age infants and low-birth-weight infants, but not for Cesarean section (248). However, the number of intervention trials is currently too limited to draw conclusions as to whether vitamin D supplementation during pregnancy might reduce the incidence of the above-mentioned adverse outcomes (249).

Gestational diabetes mellitus

Abnormal hyperglycemia due to pancreatic β-cell dysfunction characterizes the onset of gestational diabetes mellitus (GDM) in pregnant women without known type 2 diabetes mellitus. This condition is associated with serious adverse maternal outcomes, including preeclampsia, high risk of Cesarean delivery, and life-long increased risk of developing metabolic syndrome and type 2 diabetes mellitus. GDM may also contribute to increased risks of fetal macrosomia (excessive birth weight), neonatal hypoglycemia, infant respiratory distress, and increased life-long risk for obesity, glucose intolerance, type 2 diabetes mellitus, and cardiovascular disease in the offspring (reviewed in 250).

A recent prospective study conducted in 655 pregnant women found that the mean serum 25-hydroxyvitamin D concentration during the first trimester of pregnancy was significantly lower in 54 women who developed incident GDM compared to the rest of the cohort (23 ng/mL vs. 25.4 ng/mL). After multiple adjustments for confounding factors of vitamin D status and GDM risk (including overweight/obesity and prior history of type 2 diabetes and GDM), the study found each 7.5 ng/mL decrease in serum 25-hydroxyvitamin D concentration during early pregnancy was associated with a 48% higher risk of developing GDM (251). Low serum 25-hydroxyvitamin D concentrations (<29.4 ng/mL) during the second trimester of pregnancy were also associated with GDM incidence in a nested case-control study of 118 women with GDM and 219 matched control subjects (252). Five meta-analyses (248, 253-256), including observational studies of moderate-to-high quality, also reported that maternal serum vitamin D concentrations during pregnancy were inversely related to the risk of developing GDM despite evidence of bias amongst studies, such as the use of different methods for serum 25-hydroxyvitamin D measurement, measures done in different trimesters, and different criteria to assess GDM (reviewed in 257).

Further, evidence for the role of vitamin D in glucose regulation during pregnancy was reported in a small randomized, double-blind, placebo-controlled trial in 54 pregnant women diagnosed with GDM. The supplementation with 50,000 IU of vitamin D$_3$ twice during a six-week period (at day 1 and day 21) resulted in significantly lower fasting plasma glucose and serum insulin concentration, reduced insulin resistance, and improved insulin sensitivity compared to placebo (258). This suggests that vitamin D deficiency may adversely affect glucose tolerance during pregnancy and contribute to the onset of GDM. Yet, the potential benefits of vitamin D supplementation in the prevention of glucose intolerance and GDM during pregnancy have not been assessed. A multicentered, randomized controlled trial (DALI) is ongoing in Europe to evaluate the effects of vitamin D and lifestyle interventions (healthy eating and physical activity) on the metabolic status of pregnant women at risk of GDM (inclusion criteria: pre-pregnancy BMI ≥29 kg/m^2) (259). Preliminary findings suggest that healthy eating and physical activity can help lower gestational weight gain, when compared to standard-of-care; however, these lifestyle changes are unlikely to reduce the risk of GDM among obese pregnant women (260). The results regarding the effect of vitamin D supplementation in the DALI study are yet to be published.

Health outcomes in offspring

During pregnancy, increased intestinal calcium absorption and mobilization of calcium from the skeleton allows accretion of calcium within the fetal skeleton. Yet, observational studies that examined the relationship between maternal vitamin D status and measures of fetal bone growth have not provided consistent results (261, 262). In addition, recent data from the Maternal Vitamin D Osteoporosis Study (MAVIDOS) suggested no difference in whole-body bone mineral content (BMC) of newborns from mothers randomized to daily supplementation with either vitamin D$_3$ (1,000 IU) or placebo from <17 weeks' gestation until delivery (263). Further, the risk of fracture in Danish children ages 10 to 18 years was similar regardless of whether their mothers were exposed to extra vitamin D from fortification during pregnancy (264). While maternal vitamin D supplementation during pregnancy effectively prevents the neonate's risk of vitamin D deficiency at birth (265), there is little evidence that neonatal vitamin D status influences the risk of fracture later during childhood (266).

A few observational studies have given rather weak evidence in support of a relationship between maternal vitamin D sufficiency during pregnancy and incidence of respiratory conditions and allergies in children (267). A randomized controlled trial found that the supplementation of 108 pregnant women in the third trimester (at week 27 of gestation until delivery) with either 800 IU/day or a bolus dose of 200,000 IU of vitamin D$_3$ did not decrease the risk of wheezing, allergic rhinitis, food allergy diagnosis, lower respiratory tract infections, or eczema in offspring at three years of age compared to placebo (N=50) (268). A more recent double-blind, randomized controlled trial found that vitamin D$_3$ supplementation of 295 Danish pregnant women, from weeks 22 to 26 of gestation until delivery, with 2,800 IU/day (70 μg/day) — compared to 400 IU/day (10 μg/day) of vitamin D$_3$ (i.e., the current recommendation in Denmark) (N=286) — reduced the risk of troublesome episodes of lung symptoms by 17% in offspring during the first three years of life (269). However, no differences were reported regarding the risk of persistent wheeze, asthma, allergic sensitization, respiratory tract infections, or eczema between treatment and control groups (269). In a similar randomized, double-blind, controlled trial — the Vitamin D Antenatal Asthma Reduction Trial — conducted in 777 US pregnant women with a history of asthma, allergic rhinitis, or eczema (or whose partner had such an history), supplementation with 2,400 IU/day (60 μg/day) or 400 IU/day (10 μg/day) did not result in differences in the risk of developing asthma or recurrent wheezing in their children at age three years (270). Despite the lack of significance reported in individual studies, the pooled analysis of the three trials found a 19% reduction in the risk of recurrent wheeze in children whose mothers received high-dose versus low-dose vitamin D supplementation during pregnancy (271). In a cohort of 378 mother-child pairs, high serum 25-hydroxyvitamin D concentrations measured in the 34th week of pregnancy were associated with an increase in food allergy of the child during the first two years of life, warranting careful evaluation of the safety of vitamin D supplementation during pregnancy (272).

Since vitamin D insufficiency has been linked to autoimmunity (see Autoimmune diseases), it has also been proposed that poor maternal vitamin D status during pregnancy may contribute to an increased risk of autoimmune diabetes (insulin-dependent type 1 diabetes mellitus) in the offspring. Yet, the results of a study of 3,723 children at high genetic risk for type 1 diabetes and followed for a mean 4.3 year-period found that maternal intake of vitamin D (from food and/or supplements) during the third trimester of pregnancy (assessed through food frequency questionnaires) was not associated with advanced β-cell autoimmunity or clinical diabetes (142). In a nested case-control study, there was no difference in mean serum concentration of 25-hydroxyvitamin D during the first trimester of pregnancy between 343 mothers of children with type 1 diabetes and 343 control mothers (143). A follow-up study suggested that specific maternal *VDR* polymorphisms, rather than vitamin D status, may be linked to an increased susceptibility to developing type 1 diabetes in children (273). Another nested case-control study (119 mothers of children with type 1 diabetes and 129 control mothers) found an inverse association between maternal vitamin D-binding protein — but not 25-hydroxyvitamin D — concentration during the third trimester of pregnancy and the risk of type 1 diabetes in children (274). At present, there is no established causality between maternal vitamin D status during pregnancy and risk of autoimmune disease in offspring.

Acute respiratory infections

More than 200 viruses are responsible for causing familiar infections of the upper respiratory tract (URT), known as the common cold, resulting in symptoms of nasal congestion and discharge, cough, sore throat, and sneezing (275). The analysis of cross-sectional data from 18,883 participants (ages 12 years and older) of the Third US National Health and Nutrition Examination Survey (NHANES III) reported an inverse relationship between serum 25-hydroxyvitamin D concentrations and recent (self-reported) URT infection (URTI). Compared to levels of circulating vitamin D of 30 ng/mL or above, the risk of URTI was 24% higher in individuals with concentrations between 10 and 29 ng/mL and 36% higher in those with levels below 10 ng/mL (276). A subgroup analysis indicated that low concentrations of serum 25-hydroxyvitamin D in subjects with asthma and chronic obstructive pulmonary disease (COPD) were linked to a greater susceptibility to URTI when compared to people without pulmonary disease.

In a randomized, double-blind, placebo-controlled trial conducted in 322 healthy adults (ages ≥18 years), supplementation with monthly doses of vitamin D$_3$ (200,000 IU for the first two months and 100,000 IU for the following 16 months) significantly raised the mean serum 25-hydroxyvitamin D concentration (from 29 ng/mL to 48 ng/mL) in the intervention group but did not decrease the occurrence of URTI compared to placebo (277). Moreover, in a larger, multicenter, four-arm clinical trial in 2,259 subjects (aged 45-75 years) with a history of colorectal adenoma, daily vitamin D$_3$ supplementation of 1,000 IU did not reduce the number or the duration of URTI episodes during winter or the rest of the year, even among participants with the lowest serum 25-hydroxyvitamin D concentrations at baseline (278). In addition, the post-hoc analysis of data from a randomized, placebo-controlled trial in 644 individuals (ages 60-84 years) found that monthly supplementation with 30,000 IU or 60,000 IU of vitamin D$_3$ for a maximum period of one year did not significantly decrease the rate of antibiotic prescriptions for bacterial airway infections. The stratified analysis, however, found that doses of 60,000 IU/month reduced the risk of using antibiotics in participants ≥70 years old by 47% (279). In addition, compared to placebo, the supplementation of pregnant women with vitamin D$_3$ (with 2,000 IU/day) for three months until birth followed by the supplementation of their infants (800 IU/day) from birth to six months of age significantly reduced the number of acute respiratory infections after the intervention period in children 6 to 18 months old (280). Interestingly, despite significant heterogeneity among trials, the pooled analysis of these data with that of 21 additional trials suggested an overall 12% reduction in incidence of URTI with vitamin D$_3$ given as bolus doses (every week, month, or every three months), daily doses, or a combination of bolus and daily doses (281). Subgroup analyses revealed a 42% reduction in URTI risk with vitamin D$_3$ supplementation in subjects with baseline serum 25-hydroxyvitamin D concentrations <10 ng/mL, while there was no protective effect of vitamin D$_3$ in those with concentrations ≥10 ng/mL. Moreover, large bolus doses (≥30,000 IU) were found to be ineffective compared to daily or weekly doses such that, in subgroup analyses that excluded bolus doses, daily and weekly vitamin D$_3$ regimens appeared to be protective against URTI regardless of baseline vitamin D status. Finally, the effect of vitamin D$_3$ supplementation on URTI did not appear to vary with age, BMI, the presence of asthma or COPD, and flu vaccination status (281).

The findings of a large clinical trial in New Zealand, the Vitamin D Assessment (ViDA) Study, confirmed the ineffectiveness of large bolus doses of vitamin D in reducing the risk of acute respiratory infections (282). In this double-blind, placebo-controlled trial in 5,110 older adults (ages 50-84 at baseline), supplementation with an initial dose of 200,000 IU of vitamin D$_3$ followed by 100,000 IU/month of vitamin D$_3$ for a median of 3.3 years had no effect on the incidence of (self-reported) acute respiratory infections (HR, 1.01; 95% CI, 0.94-1.07). Upon data stratification by vitamin D status, a similar null result (HR, 1.08; 95% CI, 0.95-1.23) was seen in study participants with blood vitamin D concentrations ≤20 ng/mL (≤50 nmol/L; 282).

The recently completed VITAL (Vitamin D and Omega-3 Trial) may provide additional evidence of an effect of daily dosing (2,000 IU/day of vitamin D) on risk of airway infections in older adults, although the prevention of infectious disease is a secondary outcome in the trial (204, 283, 284).

In a trial in preschool-age children, vitamin D supplementation with 2,000 IU/day for at least four months did not decrease the incidence (285) or severity (286) of URTI in winter compared to supplementation with 400 IU/day for at least four months. Supplementation with 2,000 IU/day led to significantly higher mean serum 25-hydroxyvitamin D concentrations compared to the lower dose (48.7 ng/mL vs. 36.8 ng/mL), but the 400 IU dose may have been sufficient to prevent URTI in these young children (285). In a placebo-controlled trial in 1,300 healthy children and adolescents in rural Vietnam (baseline 25-hydroxyvitamin D concentrations of 26 ng/mL for both the control and intervention group), supplementation with 14,000 IU/week of vitamin D for eight months significantly reduced the incidence of non-influenza viral respiratory infections by 24%, but not the incidence of influenza A or B infection (287).

Coronavirus disease, COVID-19

The coronavirus disease, COVID-19, is caused by infection with the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). This virus originated in Wuhan, China in late 2019 and rapidly spread throughout the world causing a global pandemic. Flu-like symptoms, including cough, fever, fatigue, and difficulty breathing, as well as several other diverse symptoms characterize COVID-19 (see the websites of the CDC and the WHO). The effects of the disease vary widely, with the most severe resulting in pneumonia, respiratory distress, and death. Some individuals infected with SARS-CoV-2, however, are asymptomatic but can transmit virus to others (288). Moreover, SARS-CoV-2 infected individuals can spread disease before they experience symptoms (i.e., presymptomatic transmission) (289), placing importance on public health measures like hand washing, face mask wearing, social distancing, and testing and contact tracing to curtail the pandemic.

A number of observational studies have examined the correlation of vitamin D status and COVID-19 incidence, with most — but not all (290-292) — finding vitamin D deficiency or insufficiency associated with an increased risk of SARS-CoV-2 infection. In a retrospective cohort study of more than 191,000 US residents administered a SARS-CoV-2 test during a three-month period in spring 2020, SARS-CoV-2 positivity was strongly associated with a lower serum 25-hydroxyvitamin D concentration, measured at a single point in the 12 months prior to the viral test (293). In this study, each 1 ng/mL increment of serum 25-hydroxyvitamin D was linked to a 1.6% lower risk of SARS-CoV-2 positivity, with the risk being the lowest at serum concentrations of 55 ng/mL and above (293). In a retrospective, population-based study among 7,807 people in Israel, including 782 SARS-CoV-2 positive cases, plasma 25-hydroxyvitamin D concentrations below 30 ng/mL were associated with a 50% higher risk of SARS-CoV-2 infection compared to higher vitamin D concentrations (294). The vitamin D status assessment in this study was done prior to the viral testing, but details on the time frame are lacking. The temporal relationship of the vitamin D status measure and COVID diagnostic test is also a concern in an analysis of a large dataset from the UK Biobank, which found vitamin D status was not associated with SARS-CoV-2 infection: the study utilized vitamin D status assessments done 10 to 14 years prior to the COVID-19 diagnostic test (291). Consistent with findings of most available studies, a small retrospective cohort study (295) and five case-control studies (296-300) reported an inverse association of vitamin D status and SARS-CoV-2 infection. A 2021 meta-analysis of 10 observational studies, including 361,934 participants, reported an association between vitamin D insufficiency or deficiency and increased risk of COVID-19 (OR, 1.43; 95% CI: 1.00-2.05), although heterogeneity across studies was high (301). Further, in an analysis of data from the UK Biobank, regular use of vitamin D supplements was found to be associated with a 34% lower risk of SARS-CoV-2 infection compared nonusers of vitamin D supplements (292).

Additionally, most of the available observational research suggests an association between low vitamin D status and COVID-19 severity, with studies finding vitamin D deficiency linked to an increased risk of disease severity, as measured by need for hospitalization, intensive care unit admission (302), stage of pneumonia (in men but not in women; 303), need for non-invasive ventilation (304), need for invasive mechanical ventilation (305), or a combination of these and other indicators (297). Another study found that insufficient vitamin D status, defined as plasma 25-hydroxyvitamin D concentrations below 30 ng/mL, was associated with an increased likelihood of COVID-related hospitalization, but the association failed to reach statistical significance (p=0.061) except in a subanalysis of individuals over 50 years of age (OR, 2.71; 95% CI: 1.55-4.78; p<0.001) (294). In contrast to most of the evidence to date, one case-control study found vitamin D deficiency was not linked to COVID-19 severity (298). Further, a few studies have looked at the relationship of vitamin D status and COVID-19 mortality, with three finding vitamin D deficiency to be associated with an increased risk of death (303, 305, 306) and two finding no association (304, 307), although one of the studies finding no association used vitamin D status measurements more than 10 years prior to the COVID-19 diagnostic testing (307).

Since there are several known risk factors for severe illness from COVID-19, including advanced age, obesity, and preexisting type 2 diabetes or cardiovascular disease (308), it is important for observational studies to control for potential confounders. Two quasi-experimental studies reported that bolus supplementation with vitamin D$_3$ (either 50,000 IU per month or 80,000-100,000 IU every two to three months) prior to or during SARS-CoV-2 infection was associated with a less severe illness and improved survival in frail elderly COVID-19 patients (309, 310). A number of randomized controlled trials of vitamin D supplementation in COVID-19 prevention and treatment are currently underway; the results of these trials will inform on the causality of the association. Nevertheless, the currently available data indicate that improving vitamin D status through supplementation represents a modifiable risk factor for COVID-19.

Disease Treatment

Atopic dermatitis

Atopic dermatitis or eczema is particularly prevalent in industrialized countries, affecting 10%-20% of children and 1%-3% of adults. Atopic dermatitis is a chronic inflammatory skin disorder characterized by dry and pruritus (itchy) areas of the skin in affected subjects. Local skin inflammation and immune dysfunction can damage the epidermal barrier and increase the susceptibility to skin infections and atopic reactions in affected individuals. The disease is often associated with other atopic diseases, including food allergies, asthma, and allergic rhinitis (311).

While the etiology of the disease is not fully elucidated, it has been suggested that vitamin D deficiency might contribute to the onset and/or the severity of the disease (312). Recently, using large-scale datasets from Caucasian people of European descent, including the UK Biobank resource (313) and the SUNLIGHT (35), the GABRIEL asthma (314), and EAGLE eczema (315) consortia, a Mendelian randomization study found no association between genetically low serum 25-hydroxyvitamin D concentrations and risks of atopic dermatitis, asthma, or high serum immunoglobulin (Ig)-E concentrations (316).

A number of randomized controlled studies have examined whether vitamin D might be an effective adjunct tool in disease management, possibly through regulating local inflammatory reactions and stimulating antimicrobial activities in the skin. Moreover, the beneficial effect of phototherapy observed in specific cases of atopic dermatitis may be partly mediated by the action of vitamin D (311). In a small randomized, double-blind, placebo-controlled study in 45 patients with atopic dermatitis and low vitamin D status (70% of subjects had serum 25-hydroxyvitamin D concentrations <20 ng/mL), daily administration of 1,600 IU of oral vitamin D$_3$, alone or together with 600 IU/day of vitamin E, for a period of 60 days significantly reduced the extent and intensity of eczema, as assessed by the SCORAD (SCORing Atopic Dermatitis) score (317). Vitamin D$_3$ (1,600 IU/day for 60 days) also improved vitamin D status and reduced disease severity in 53 patients with atopic dermatitis in another small randomized trial (318). More recently, vitamin D$_3$ (1,000 IU/day for one month) improved the severity of winter-related atopic dermatitis in Mongolian children, as shown by changes in Eczema Area and Severity Index (EASI) and Investigator's Global Assessment (IGA) scores (319). A meta-analysis of four small trials (including those cited above) confirmed that supplemental vitamin D can lead to measurable clinical improvements in affected individuals (320). Larger trials are needed to strengthen these preliminary findings and determine the most appropriate and effective supplementation regimen. Of note, topical treatment of psoriasis with vitamin D analogs has been approved by the US Food and Drug Administration (FDA) and may be effective in the management of other skin disorders (321).

Inflammatory bowel diseases

Several ill-defined environmental and genetic factors are thought to contribute to the development of the inappropriate immune response to the intestinal microbiota that causes ulcerative colitis (UC) and Crohn's disease (CD). While specific *VDR* polymorphisms may be linked to an increased susceptibility to developing UC and CD (322), higher vitamin D intakes and predicted circulating levels were found to be associated with a reduced incidence of UC and CD in a large cohort of 72,719 women (323). A meta-analysis of six observational studies found an inverse association between vitamin D status and severity of CD (324). Three studies have investigated whether vitamin D$_3$ could benefit patients with CD, possibly through reducing intestinal inflammation. In one multicenter, double-blind, placebo-controlled study, the relapse rate in CD patients in remission after one year of treatment was significantly lower in those supplemented daily with 1,200 IU of vitamin D$_3$ and 1,200 mg of calcium compared to those who received calcium alone (13% vs. 29%) (325). In a second pilot study, incremental daily doses of vitamin D$_3$, from 1,000 IU up to 5,000 IU, were administrated over a 24-week period to 18 CD patients in order to achieve circulating 25-hydroxyvitamin D concentrations >40 ng/mL. Although half of the patients failed to achieve 40 ng/mL, the mean 25-hydroxyvitamin D concentration was raised to 45 ng/mL (from a baseline mean of 16 ng/mL), and the overall improvement in vitamin D status was associated with a significant decrease in disease severity as assessed by Crohn's Disease Activity (CDAI) scores (326). In a three-month, randomized, double-blind, placebo-controlled trial in 27 CD patients in remission, daily supplementation with vitamin D$_3$ (2,000 IU) improved vitamin D status but had no significant effect on intestinal permeability ('leaky gut') or measures of inflammation and disease activity (327). Yet, the study suggested that achieving serum 25-hydroxyvitamin D concentrations ≥30 ng/mL might help reduce intestinal inflammation and improve patients' quality of life. Additional studies are needed to confirm the therapeutic efficacy of vitamin D in inflammatory bowel diseases.

Cardiovascular disease

The prospective analysis of 41,504 electronic medical records in the Intermountain Heart Collaborative study found that only one-third of patients had adequate serum 25-hydroxyvitamin D concentrations (>30 ng/mL); vitamin D insufficiency (serum 25-hydroxyvitamin D concentrations ≤30 ng/mL) was associated with increased prevalence and incidence of many cardiovascular conditions, including hypertension, coronary artery disease, heart failure, and stroke (328). Suboptimal vitamin D status has also been linked to arterial stiffness and vascular endothelial dysfunction — strong determinants of incident hypertension and adverse cardiovascular outcomes (329).

Hypertension

Several intervention studies have evaluated the effect of vitamin D supplementation on blood pressure. An early controlled clinical trial in 18 men and women with untreated mild hypertension living in the Netherlands found that exposure to UVB radiation three times weekly for six weeks during the winter increased serum 25-hydroxyvitamin D concentrations by 162%, lowered PTH concentrations by 15%, and decreased 24-hour ambulatory systolic and diastolic blood pressure measurements by an average of 6 mm Hg (330). A recent meta-analysis of 16 randomized controlled trials involving 1,879 participants, either healthy or with pre-existing cardiometabolic conditions (including hypertension), found no significant reduction in systolic and diastolic blood pressures with vitamin D supplementation (800-8,571 IU/day for five weeks to one year). However, a subgroup analysis of six trials found a significant reduction of 1.31 mm Hg in diastolic blood pressure in individuals with preexisting conditions. While improvements in blood pressure may be expected in cases of vitamin D insufficiency/deficiency, the authors noted that suboptimal vitamin D status in participants was not exclusively observed in those with cardiometabolic conditions (331). In contrast, in two recent intervention studies — the Styrian vitamin D hypertension trial (332) and the Vitamin D therapy in individuals at high risk of hypertension trial [DAYLIGHT] (333) — subjects with (pre)hypertension supplemented with vitamin D$_3$ (400 to 4,000 IU/day for two to six months) showed no evidence of blood pressure lowering, regardless of their baseline vitamin D status (insufficient or adequate, according to the IOM's current cutoffs).

Conditions that decrease vitamin D synthesis in the skin, such as having dark-colored skin, living in temperate latitudes, and aging, are associated with increased prevalence of hypertension (334), suggesting that vitamin D may reduce blood pressure levels in selected groups of individuals. In the above-mentioned meta-analysis, one four-arm, double-blind, placebo-controlled clinical trial was conducted in 283 African Americans randomized to receive daily vitamin D$_3$ supplements of 1,000 IU, 2,000 IU, or 4,000 IU for a period of three months. Systolic blood pressure was decreased by 0.66 mm Hg with 1,000 IU/day, 3.4 mm Hg with 2,000 IU/day, and by 4 mm Hg with 4,000 IU/day while it increased by 1.7 mm Hg in the placebo group when compared to baseline. A significant reduction of 0.2 mm Hg in systolic blood pressure was detected per 1 ng/mL incremental increase in 25-hydroxyvitamin D concentration. However, there was no statistical difference on three-month change in blood pressure between vitamin D$_3$ and placebo (335). Another randomized, placebo-controlled study in 150 elderly participants (mean age, 77 years) showed that supplementation with 100,000 IU of vitamin D$_3$ every three months for one year did not significantly lower blood pressure compared to placebo (336).

Further research is needed to determine whether vitamin D supplementation is helpful in the prevention or management of hypertension.

Congestive heart failure

Congestive heart failure (also called cardiac insufficiency) is characterized by increased heart rate and subsequent hypertrophy of the left heart ventricle. Cardiac insufficiency is associated with a reduced left ventricular ejection fraction (LVEF), assessed by echocardiography. Inhibitors of angiotensin-converting enzyme (ACE) (see Blood pressure regulation) are currently used as first-line therapy for patients with heart failure. In a cross-sectional study in healthy patients who underwent coronary angiography, serum 25-hydroxyvitamin D concentrations <30 ng/mL were associated with poorer coronary flow rates (337). Suboptimal vitamin D status has also been linked to poorer prognosis in patients with heart failure (338). Over the past several years, a number of intervention studies have examined the effect of vitamin D supplementation in those with cardiac insufficiency. In a 12-week randomized, double-blind, placebo-controlled study, daily supplementation with 1,200 IU of vitamin D$_3$ in children with chronic congestive heart failure led to a significant increase in vitamin D status accompanied by an improved heart muscle performance (increased LVEF), as well as by lower levels of PTH and pro-inflammatory cytokines (339). In another randomized, double-blind, placebo-controlled trial in 64 elderly patients with heart failure, participants receiving 800 mg/day of calcium and 50,000 IU/week of vitamin D$_3$ did not perform significantly better at physical performance tasks (used as proxy to assess aerobic capacity and skeletal muscle strength) compared to those supplemented with calcium only (340). A recent meta-analysis of seven small randomized placebo-controlled trials in 573 subjects with heart failure showed that vitamin D supplementation (from 1,000 IU/day to 50,000 IU/week) for six weeks to nine months could reduce serum concentrations of PTH, tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP). Yet, there were no significant differences in LVEF, circulating interleukin-10 (IL-10) concentration, and renin concentration between patients treated with vitamin D and those given a placebo (341). Finally, in the EVITA (Effect of vitamin D on all-cause mortality) trial in patients with end-stage heart failure and inadequate vitamin D status (baseline serum 25-hydroxyvitamin D values, 8.6-19.7 ng/mL), supplementation with 4,000 IU/day for three years did not reduce the risk of mortality compared to placebo (342).

Sources

Sunlight

Solar ultraviolet-B radiation (UVB; wavelengths of 290 to 315 nanometers) stimulates the production of vitamin D$_3$ in the epidermis of the skin (343). Sunlight exposure can provide most people with their entire vitamin D requirement. Children and young adults who spend a short time outside two or three times a week will generally synthesize all the vitamin D they need to prevent deficiency. One study reported that serum vitamin D concentrations following exposure to one minimal erythemal dose of simulated sunlight (the amount required to cause a slight pinkness of the skin) to the whole body was equivalent to ingesting approximately 10,000 to 25,000 IU of vitamin D (344). People with dark-colored skin synthesize markedly less vitamin D on exposure to sunlight than those with lighter complexion (34). Additionally, older adults have diminished capacity to synthesize vitamin D from sunlight exposure and frequently use sunscreen or protective clothing in order to prevent skin cancer and sun damage. The application of sunscreen with an SPF factor of 10 reduces production of vitamin D by 90% (30). In latitudes around 40 degrees north or 40 degrees south (Boston is 42 degrees north), there is insufficient UVB radiation available for vitamin D synthesis from November to early March. Ten degrees farther north or south (Edmonton, Canada), the "vitamin D winter" extends from mid-October to mid-March. It has been estimated that up to 15 minutes of daily sun exposure on the hands, arms, and face around 12 pm throughout the year at 25 degrees latitude (Miami, FL) and during the spring, summer, and fall at 42 degrees (Boston, MA) latitude may provide a light-skinned individual with 1,000 IU of vitamin D (345).

Food sources

Vitamin D is found naturally in only a few foods, such as some fatty fish (mackerel, salmon, sardines), fish liver oils, eggs from hens that have been fed vitamin D, and mushrooms exposed to sunlight or UV light. In the US, milk and infant formula are fortified with vitamin D so that they contain 400 IU (10 μg) per quart. However, other dairy products, such as cheese and yogurt, are not always fortified with vitamin D. Some cereal, bread, and fruit juices may also be fortified with vitamin D. Accurate estimates of average dietary intakes of vitamin D are difficult because of the high variability of the vitamin D content of fortified foods (346). The vitamin D content (sum of vitamin D$_2$ and vitamin D$_3$) of some vitamin D-rich foods is listed in **Table 2** in both international units (IU) and micrograms (μg). For more information on the nutrient content of specific foods, search USDA's FoodData Central. The 25-hydroxyvitamin D metabolite is also present at low levels is certain foods, including meats, dairy products, and eggs (347, 348).

Table 2. Some Food Sources of Vitamin D

Food	Serving	Vitamin D (IU)	Vitamin D (μg)
Pink salmon, canned	3 ounces	465	11.6
Mackerel, canned (boneless)	3 ounces	248	6.2
Sardines, canned	3 ounces	164	4.1
Milk, low-fat (1%), fortified with vitamin D	8 fluid ounces	108	2.7
Orange juice, fortified with vitamin D	8 fluid ounces	100	2.5
Cereal, fortified	1 serving (usually 1 cup)	40-50	1.0-1.3
Egg yolk	1 large	37	0.9

Supplements

Most vitamin D supplements available without a prescription contain cholecalciferol (vitamin D$_3$). Multivitamin supplements generally provide 400 IU-1,000 IU (10 μg-25 μg) of vitamin D$_2$ or vitamin D$_3$. Single-ingredient vitamin D supplements may provide 400 to 50,000 IU of vitamin D$_3$, but 400 IU is the most commonly available dose (66). A number of calcium supplements may also provide vitamin D. A meta-analysis of randomized controlled trials suggested that bolus doses of vitamin D$_2$ (ergocalciferol) may not always be as effective as vitamin D$_3$ in raising serum 25-hydroxyvitamin D concentrations, yet no difference in efficacy was found with daily supplementation with vitamin D$_2$ or vitamin D$_3$ (349). Nonetheless, a 25-week, randomized, double-blind, placebo-controlled trial found daily supplementation with 1,000 IU of vitamin D$_3$ initiated at the end of summer to be more efficacious than vitamin D$_2$ in maintaining summertime concentrations of 25-hydroxyvitamin D during fall and winter months (350).

There is growing interest in using the hydroxylated form of cholecalciferol, 25-hydroxyvitamin D$_3$ (calcidiol; calcifediol), as a supplement. This vitamin D metabolite is synthesized by the liver of humans and animals from cholecalciferol produced in skin or consumed in the diet, and is present in some foods (e.g., meats, milk, eggs) at low levels (347, 348). In general, clinical studies have found calcifediol is two to five times more potent at increasing blood concentrations of 25-hydroxyvitamin D compared to supplementation with equivalent doses of cholecalciferol (351-359). Supplementation with calcifediol may thus represent a means to improve vitamin D status rapidly and consistently with lower doses than cholecalciferol and may benefit those individuals with conditions that decrease intestinal absorption of cholecalciferol (359). However, the 25-hydroxyvitamin D$_3$ form is presently not available as an over-the-counter supplement in the United States.

Safety

Toxicity

Vitamin D toxicity (hypervitaminosis D) has not been observed to result from sun exposure. The reason is that excessive sunlight exposure generates a number of biologically inert photoproducts from 7-dehydrocholesterol and cholecalciferol (3). Vitamin D toxicity induces abnormally high serum calcium concentration (hypercalcemia), which could result in bone loss, kidney stones, and calcification of organs like the heart and kidneys if untreated over a long period of time. Hypercalcemia has been observed following daily doses of greater than 50,000 IU of vitamin D (360). Overall, research suggests that vitamin D toxicity is very unlikely in healthy people at intake levels lower than 10,000 IU/day (361-363). However, the Food and Nutrition Board of the IOM conservatively set the tolerable upper intake level (UL) at 4,000 IU/day (100 μg/day) for all adults (**Table 3**). Certain medical conditions can increase the risk of hypercalcemia in response to vitamin D, including primary hyperparathyroidism, sarcoidosis, tuberculosis, and lymphoma (361). People with these conditions may develop hypercalcemia in response to any increase in vitamin D nutrition and should consult a qualified health care provider regarding any increase in vitamin D intake.

Table 3. Tolerable Upper Intake Level (UL) for Vitamin D

Age Group	μg/day	IU/day
Infants 0-6 months	25	1,000
Infants 6-12 months	37.5	1,500
Children 1-3 years	62.5	2,500
Children 4-8 years	75	3,000
Children 9-13 years	100	4,000
Adolescents 14-18 years	100	4,000
Adults 19 years and older	100	4,000

Drug interactions

The following medications should not be taken at the same time as vitamin D because they can decrease the intestinal absorption of vitamin D: cholestyramine (Questran), colestipol (Colestid), orlistat (Xenical), and mineral oil (364, 365). The following medications increase the metabolism of vitamin D and may decrease serum 25-hydroxyvitamin D concentrations: phenytoin (Dilantin), fosphenytoin (Cerebyx), phenobarbital (Luminal), carbamazepine (Tegretol), and rifampin (Rimactane) (6). Cimetidine, a H$_2$ blocker that suppresses stomach acid secretion, inhibits the hydroxylation of vitamin D in the liver (366). Treating acid reflux, gastroesophageal reflux disease (GERD), or ulcers with proton-pump inhibitors (omeprazole, lansoprazole) might interfere with calcium absorption and increase the risk of fracture such that patients are advised to take calcium and vitamin D supplements (367). The oral antifungal medication, ketoconazole, inhibits the 25-hydroxyvitamin D$_3$-1α-hydroxylase enzyme and has been found to reduce serum 1α,25-dihydroxyvitamin D concentrations in healthy men (368). The Endocrine Society also recommends monitoring vitamin D status of patients on glucocorticoids and HIV treatment drugs because these medications increase the catabolism of 25-hydroxyvitamin D (40). The use of some cytostatic agents (cell growth inhibitors) may also increase the degradation of 25-hydroxyvitamin D and 1α,25-dihydroxyvitamin D in cancer patients under chemotherapy (6). The induction of hypercalcemia by toxic levels of vitamin D may precipitate cardiac arrhythmia in patients on digoxin (Lanoxin) (366). Hypercalcemia may also reduce the effectiveness of verapamil (Calan) and diltiazem (Cardizem) in atrial fibrillation (366).

Linus Pauling Institute Recommendation

The Linus Pauling Institute recommends that generally healthy adults take 2,000 IU (50 μg) of supplemental vitamin D daily. Most multivitamins contain 400 IU (10 μg) of vitamin D, and single-ingredient vitamin D supplements are available for additional supplementation. Sun exposure, diet, skin color, and body mass index (BMI) have variable, substantial impact on body vitamin D levels. To adjust for individual differences and ensure adequate body vitamin D status, the Linus Pauling Institute recommends aiming for a serum 25-hydroxyvitamin D concentration of at least 30 ng/mL (75 nmol/L). Observational studies suggest that serum 25-hydroxyvitamin D concentrations between 30 ng/mL and 60 ng/mL are associated with lower risks of adverse health outcomes, including cancers and autoimmune diseases.

The American Academy of Pediatrics currently suggests that all infants, children, and adolescents receive 400 IU of supplemental vitamin D daily (19). Consistent with the recommendations of the Endocrine Society (40), the Linus Pauling Institute recommends daily intakes of 400 to 1,000 IU (10 to 25 μg) of vitamin D in infants and 600 to 1,000 IU (15 to 25 μg) of vitamin D in children and adolescents. Given the average vitamin D content of breast milk, infant formula, and the diets of children and adolescents, supplementation may be necessary to meet these recommendations.

Older adults (>50 years)

Daily supplementation with 2,000 IU (50 μg) of vitamin D is especially important for older adults because aging is associated with a reduced capacity to synthesize vitamin D in the skin upon sun exposure.

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Vitamin E

Vitamin E

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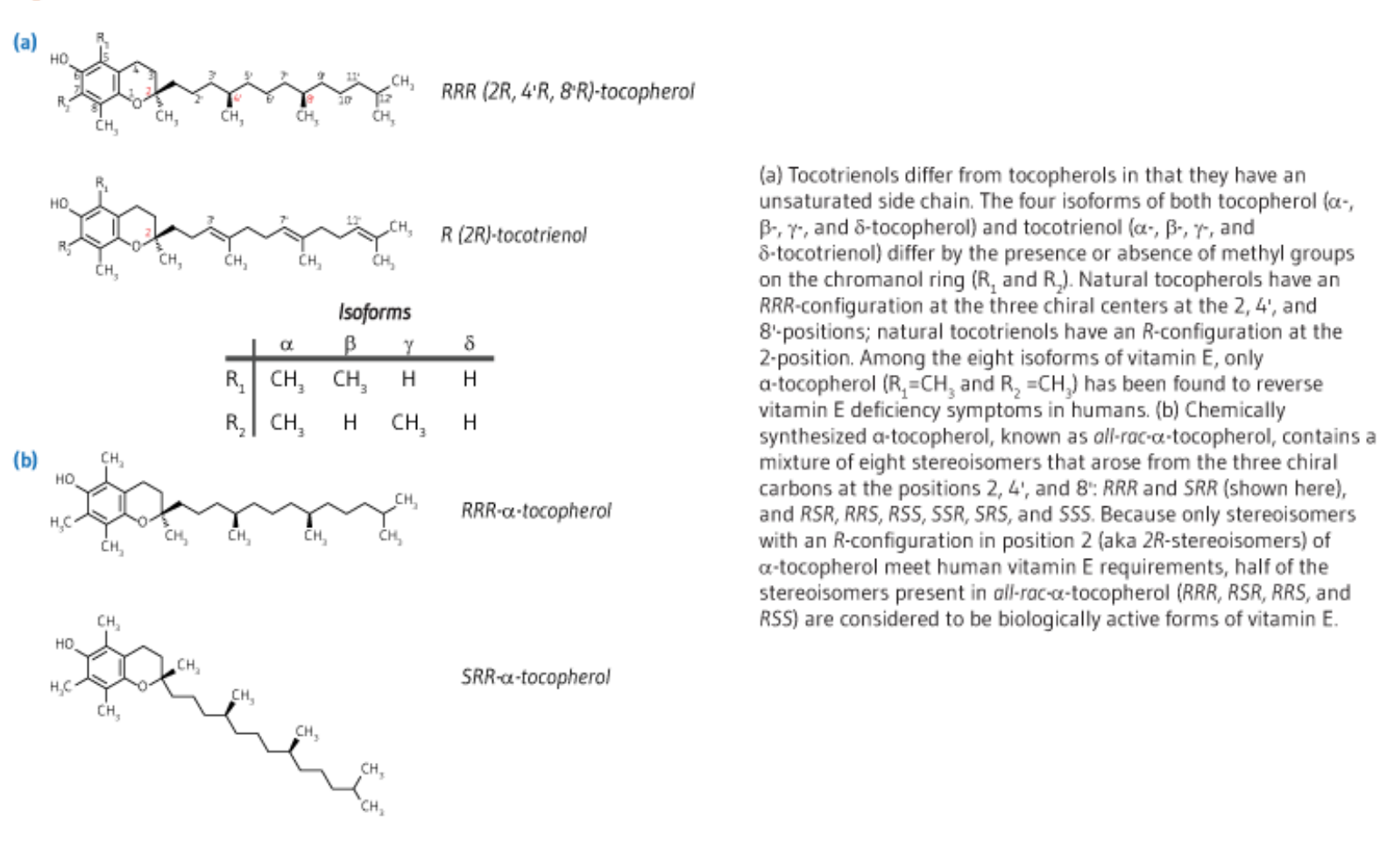
Read the Nutrition Information Brief on vitamin E by Maret G. Traber, Ph.D.

Summary

- Naturally occurring vitamin E includes eight fat-soluble isoforms: α-, β-, γ-, and δ-tocopherol and α-, β-, γ-, and δ-tocotrienol. Yet, the body preferentially uses α-tocopherol, and only α-tocopherol supplementation can reverse vitamin E deficiency symptoms. *(More information)*
- α-Tocopherol functions as a chain-breaking antioxidant, preventing the propagation of free radicals in membranes and plasma lipoproteins. α-Tocopherol is also likely involved in strengthening certain aspects of cell-mediated immunity. *(More information)*
- Vitamin E deficiency can be caused by fat malabsorption disorders or by genetic abnormalities that affect vitamin E transport. Severe deficiency symptoms include vitamin E deficiency-induced ataxia, peripheral neuropathy, muscle weakness, and damage to the retina of the eye. *(More information)*
- The current recommended dietary allowance (RDA) is 15 mg/day of α-tocopherol. It is estimated that more than 90% of Americans adults do not meet the estimated average requirement (EAR) of 12 mg/day of α-tocopherol. *(More information)*
- Randomized controlled trials investigating primary and/or secondary prevention of chronic diseases, such as cardiovascular disease, cancer, and cataracts, do not currently support a preventative effect of supplemental α-tocopherol. *(More information)*
- Limited clinical evidence suggests that vitamin E supplementation may be beneficial for managing age-related macular degeneration and fatty liver diseases secondary to type 2 diabetes mellitus. *(More information)*
- Supplementation with α-tocopherol was found to slow cognitive decline or loss of functional abilities in cognitively impaired subjects in some, but not all, clinical studies. *(More information)*
- Plant seeds, especially sunflower seeds, almonds, and hazelnuts, are rich sources of α-tocopherol such that many vegetable oils (e.g., olive oil and canola oil) also contain α-tocopherol. Other sources include tomato, avocado, spinach, asparagus, Swiss chard, and broccoli. *(More information)*
- High doses of supplemental α-tocopherol may interfere with the vitamin K-dependent blood clotting cascade and increase the risk of bleeding in individuals taking anticoagulant drugs. A tolerable upper intake level (UL) for α-tocopherol in adults is set at 1,000 mg/day and applies to all possible stereoisomers of α-tocopherol. *(More information)*

The term vitamin E describes a family of eight fat-soluble molecules with antioxidant activities: four tocopherol isoforms (α-, β-, γ-, and δ-tocopherol) and four tocotrienol isoforms (α-, β-, γ-, and δ-tocotrienol) (**Figure 1**). Only one form, α-tocopherol, meets human vitamin E requirements (see The RDA). In the human liver, α-tocopherol is the form of vitamin E that is preferentially bound to α-tocopherol transfer protein (α-TTP) and incorporated into lipoproteins that transport α-tocopherol in the blood for delivery to extrahepatic tissues. Therefore, it is the predominant form of vitamin E found in the blood and tissues (1). In addition, α-tocopherol appears to be the form of vitamin E with the greatest nutritional significance, such that it will be the primary topic of the following discussion.

Figure 1. Chemical Structures of Vitamin E Isoforms



(a) Tocotrienols differ from tocopherols in that they have an unsaturated side chain. The four isoforms of both tocopherol (α-, β-, γ-, and δ-tocopherol) and tocotrienol (α-, β-, γ-, and δ-tocotrienol) differ by the presence or absence of methyl groups on the chromanol ring (R_1 and R_2). Natural tocopherols have an *RRR*-configuration at the three chiral centers at the 2, 4', and 8'-positions; natural tocotrienols have an *R*-configuration at the 2-position. Among the eight isoforms of vitamin E, only α-tocopherol (R_1=CH_3 and R_2 =CH_3) has been found to reverse vitamin E deficiency symptoms in humans. (b) Chemically synthesized α-tocopherol, known as *all-rac*-α-tocopherol, contains a mixture of eight stereoisomers that arose from the three chiral carbons at the positions 2, 4', and 8': *RRR* and *SRR* (shown here), and *RSR*, *RRS*, *RSS*, *SSR*, *SRS*, and *SSS*. Because only stereoisomers with an *R*-configuration in position 2 (aka *2R*-stereoisomers) of α-tocopherol meet human vitamin E requirements, half of the stereoisomers present in *all-rac*-α-tocopherol (*RRR*, *RSR*, *RRS*, and *RSS*) are considered to be biologically active forms of vitamin E.

[Figure 1 - Click to Enlarge]

Function

α-Tocopherol

Natural versus synthetic α-tocopherol

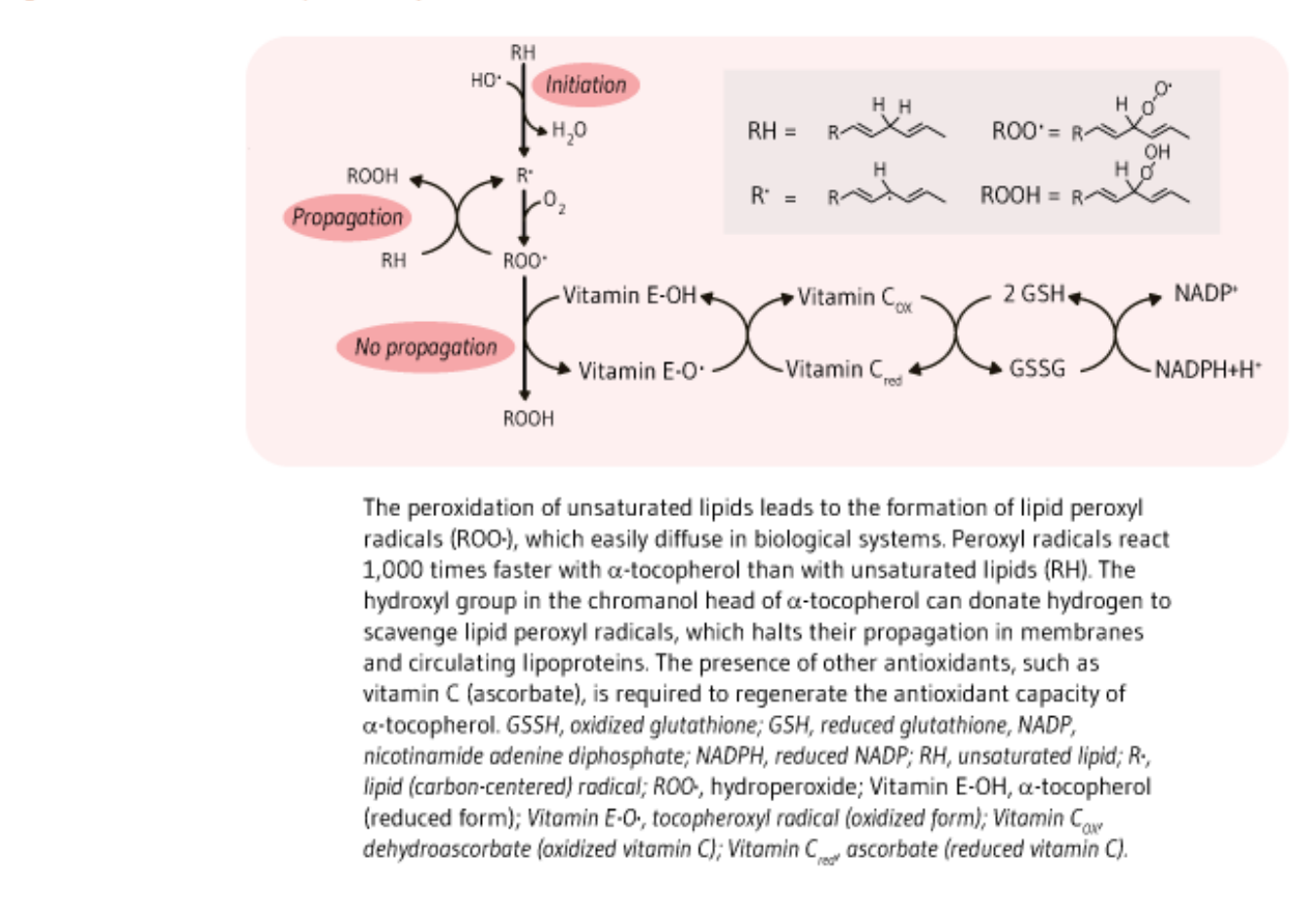
Natural α-tocopherol made by plants found in food has an *RRR*-configuration at the 2, 4', and 8'-position of the α-tocopherol molecule (wrongly referred to as *d*-α-tocopherol) (see **Figure 1**). Chemically synthesized *all-rac*-α-tocopherol (*all-racemic*-α-tocopherol; incorrectly labeled *dl*-α-tocopherol) is a mixture of eight stereoisomers of α-tocopherol, which arose from the three chiral carbons at the 2, 4', and 8'-positions: *RRR*-, *RSR*-, *RRS*-, *RSS*-, *SRR*-, *SSR*-, *SRS*-, and *SSS*-α-tocopherol (see **Figure 1**). While all stereoisomers have equal *in vitro* antioxidant activity, only the forms in the *R*-conformation at position 2 (noted 2*R*) meet the vitamin E requirements in humans (2).

Antioxidant activity

The main function of α-tocopherol in humans is that of a fat-soluble antioxidant. Fats, which are an integral part of all cell membranes, are vulnerable to damage through lipid peroxidation by free radicals. α-Tocopherol is uniquely suited to intercept peroxyl radicals and thus prevent a chain reaction of lipid oxidation (**Figure 2**). When a molecule of α-tocopherol neutralizes a free radical, it is oxidized and its antioxidant capacity is lost. Other antioxidants, such as vitamin C, are capable of regenerating the antioxidant capacity of α-tocopherol (**Figure 2**) (reviewed in 1).

Aside from maintaining the integrity of cell membranes throughout the body, α-tocopherol protects the fats in low-density lipoproteins (LDLs) from oxidation. Lipoproteins are particles composed of lipids and proteins that transport fats through the bloodstream. LDLs specifically transport cholesterol from the liver to the tissues of the body. Oxidized LDLs have been implicated in the development of cardiovascular disease (3).

Figure 2. Antioxidant Activity of α-Tocopherol



The peroxidation of unsaturated lipids leads to the formation of lipid peroxyl radicals (ROO•), which easily diffuse in biological systems. Peroxyl radicals react 1,000 times faster with α-tocopherol than with unsaturated lipids (RH). The hydroxyl group in the chromanol head of α-tocopherol can donate hydrogen to scavenge lipid peroxyl radicals, which halts their propagation in membranes and circulating lipoproteins. The presence of other antioxidants, such as vitamin C (ascorbate), is required to regenerate the antioxidant capacity of α-tocopherol. *GSSH, oxidized glutathione; GSH, reduced glutathione, NADP, nicotinamide adenine diphosphate; NADPH, reduced NADP; RH, unsaturated lipid; R•, lipid (carbon-centered) radical; ROO•,* hydroperoxide; Vitamin E-OH, α-tocopherol (reduced form); *Vitamin E-O•, tocopheroxyl radical (oxidized form); Vitamin* C_{ox}, *dehydroascorbate (oxidized vitamin C); Vitamin* C_{red}, *ascorbate (reduced vitamin C).*

[Figure 2 - Click to Enlarge]

Effects on cell-mediated immunity

Other functions of α-tocopherol are likely to be related to its antioxidant capacity (1). For instance, α-tocopherol can protect the physiological properties of lipid bilayer membranes and may influence the activity of membrane proteins and enzymes (4). In cell culture studies, α-tocopherol was found to improve the formation of an adhesive junction (known as immune synapse) between naïve T lymphocytes and antigen-presenting cells (APC), which eventually prompted T cell activation and proliferation (see Disease Prevention) (5, 6).

γ-Tocopherol and tocotrienols

Vitamin E forms other than α-tocopherol are also known to be potent antioxidants. Tocotrienols and γ-tocopherol are thought to be better scavengers of peroxyl radicals and reactive nitrogen species, respectively, than α-tocopherol (7). Yet, in the body, (1) α-tocopherol is preferentially retained in the liver by the binding to α-tocopherol transfer protein (α-TTP), which incorporates α-tocopherol into lipoproteins for delivery to extrahepatic tissues; and (2) forms of vitamin E other than α-tocopherol are actively metabolized and excreted. Hence, while γ-tocopherol is the most common form of vitamin E in the American diet (8), its plasma and tissue concentrations are generally significantly lower than those of α-tocopherol, and more γ-tocopherol is excreted in urine than α-tocopherol, suggesting less γ-tocopherol is needed for use by the body (1).

Studies conducted *in vitro* and in animals have indicated that γ-tocopherol and its major metabolite, γ-carboxyethyl hydroxychroman (γ-CEHC), may play a role in protecting the body from free radical-induced damage in various conditions of oxidative stress and inflammation (reviewed in 7). Limited intervention studies (highlighted in 7) have not convincingly demonstrated a potential anti-inflammatory effect of γ-tocopherol in humans. Yet, in two recent randomized, placebo-controlled studies, the supplementation of smokers with γ-tocopherol potentiated short-term benefits of smoking cessation (with or without nicotine replacement therapy) on vascular endothelial function (9, 10).

Numerous preclinical studies have also suggested that tocotrienols might be beneficial in the prevention of chronic diseases (11). For instance, tocotrienols (especially δ-tocotrienol) have shown greater anti-proliferative and pro-apoptotic effects than tocopherols in malignant cell lines (12). However, a number of factors, including dose, formulation, and type of study population, affect the bioavailability of tocotrienols and may undermine their putative efficacy in humans (13). There are currently no data available on the effectiveness of supplemental tocotrienols in humans (11).

Nutrient interactions

Dietary and circulating fatty acids

The mechanism of vitamin E digestion and uptake into intestinal cells (enterocytes) is unclear but requires bile acids and pancreatic enzymes, and the packaging along with dietary fat into chylomicrons. The efficiency of vitamin E absorption increases with the amount of fat in ingested food, such that vitamin E absorption from supplements is likely to be minimal with low-fat meals (14, 15).

In the circulation, all lipoproteins (i.e., VLDLs, LDLs, and HDLs) are involved in the transport and tissue distribution of α-tocopherol (1). Increased concentrations of lipids (cholesterol and triglycerides) in the blood have been correlated to higher serum α-tocopherol concentrations. However, if a high blood concentration of lipids is associated with a slower turnover of lipoproteins, then the distribution of α-tocopherol to tissues may be substantially altered (16).

Vitamin C

A few human studies using conditions of oxidative stress have demonstrated the importance of vitamin C (ascorbic acid) in the recycling of oxidized α-tocopherol back to its reduced state (see **Figure 2**). Oxidative stress caused by cigarette smoking accelerates the depletion of plasma α-tocopherol in smokers compared to nonsmokers (17). In a double-blind, placebo-controlled trial in 11 smokers and 13 nonsmokers given α-tocopherol and γ-tocopherol that was labeled with deuterium (hence traceable), supplementation with vitamin C reduced the rate of vitamin E loss in plasma, most probably by regenerating tocopheryl radicals back to nonoxidized forms (18).

Vitamin K

One study in adults with normal coagulation (clotting) status found that daily supplementation with 1,000 IU (670 mg) of *RRR*-α-tocopherol for 12 weeks decreased γ-carboxylation of prothrombin, a vitamin K-dependent factor in the coagulation cascade (19). Individuals taking anticoagulant drugs like warfarin and those who are vitamin K deficient should not take vitamin E supplements without medical supervision because of the increased risk of bleeding (see Safety) (20).

Deficiency

Causes

Severe vitamin E deficiency rarely occurs in humans but has been observed as a result of malnutrition (21). Severe vitamin E deficiency has been associated with specific genetic defects affecting the transport of α-tocopherol by α-tocopherol transfer protein (α-TTP) and lipoproteins. Vitamin E deficiency has also been observed in individuals with fat malabsorption syndromes, which impair the absorption of dietary fats and therefore fat-soluble vitamins like vitamin E (see Nutrient interactions) (21).

Symptoms

Severe vitamin E deficiency results mainly in neurologic symptoms, including impaired balance and coordination (spinocerebellar ataxia), injury to the sensory nerves (peripheral neuropathy), muscle weakness (myopathy), and damage to the retina of the eye (retinopathy). For this reason, people who develop peripheral neuropathy, ataxia, or retinitis pigmentosa (RP) of unknown causes should be screened for vitamin E deficiency (21). The results of one randomized controlled trial in 601 patients with common forms of RP indicated that daily supplementation with 400 IU of *all-rac*-α-tocopherol (180 mg of *RRR*-α-tocopherol) modestly but significantly increased the loss of retinal function (22). In contrast, daily supplementation with 15,000 IU of vitamin A (4,500 µg RAE) significantly slowed the loss of retinal function over a period of four to six years, suggesting that patients with common forms of RP may benefit from long-term vitamin A supplementation but should avoid high-dose supplemental vitamin E.

Inherited defects in α-TTP are associated with a characteristic syndrome called AVED (Ataxia with Vitamin E Deficiency). A recent case study reported that visual impairment in a middle-age patient with AVED was caused by both RP and early-onset macular degeneration (23). Supplementation with high-dose vitamin E (800-1,200 mg/day) is used to prevent neurologic deterioration in AVED subjects (21).

Moreover, the developing nervous system appears to be especially vulnerable to vitamin E deficiency. For instance, children with severe vitamin E deficiency at birth rapidly experience irreversible neurologic symptoms if not treated with vitamin E. In contrast, individuals who develop gastrointestinal disorders affecting vitamin E absorption in adulthood may not develop neurologic symptoms for 10-20 years (21). It should also be noted that neurologic symptoms caused by vitamin E deficiency have not been reported in healthy individuals who consume diets low in vitamin E.

Marginal deficiency

Although frank vitamin E deficiency is rare, marginal intake of vitamin E is relatively common. Between 1988 and 1994, the US National Health and Nutrition Examination Survey III (NHANES III) examined the dietary intake and blood concentrations of α-tocopherol in 16,295 adults. The study reported that about one-third of all participants had blood concentrations of α-tocopherol below 20 micromoles/liter (µmol/L) — a cutoff value chosen because of its initial association with an increased risk for cardiovascular disease (24). More recent data from 18,063 participants in NHANES 2003-2006 indicated an average dietary intake of α-tocopherol from food (including enriched and fortified sources) among Americans adults of 7.2 mg/day (25). This intake is well below the current recommended dietary allowance of 15 mg/day (see the RDA). At this level of dietary intake, more than 93% of American adults do not meet the estimated average requirement (EAR) of 12 mg/day for vitamin E (25). In addition, a recent nested case-control study in Bangladeshi women suggested that inadequate vitamin E status during early pregnancy may be associated with an increased risk of miscarriage (26).

Cigarette smoking is thought to increase the utilization of α-tocopherol such that smokers might be at increased risk of deficiency compared with nonsmokers (17). Also, the 19-year follow-up analysis of the Alpha-Tocopherol, Beta-Carotene cancer (ATBC) trial in older, male smokers indicated that participants in the highest versus lowest quintile of serum α-tocopherol concentrations (>31 µmol/L vs. <23 µmol/L) at baseline had reduced risks of total and cause-specific mortality (27).

It is not known whether marginal vitamin E deficiency increases the risk of chronic disease (1).

The Recommended Dietary Allowance (RDA)

The RDA for vitamin E was last revised by the Food and Nutrition Board of the US Institute of Medicine in 2000 (**Table 1**) (2). The RDA is based largely on the results of studies done in the 1950s in men fed vitamin E-deficient diets. In a test-tube analysis, vitamin E suppresses the breakdown of red blood cells (known as hemolysis) induced by hydrogen peroxide. Because hemolysis has also been reported in children with severe vitamin E deficiency, the preventive effect of vitamin E against oxidative damage-induced hemolysis was considered to be a clinically relevant *in vitro* analysis to assess vitamin E status. Importantly, this means that the latest RDA for vitamin E continues to be based on the prevention of deficiency symptoms rather than on health promotion and prevention of chronic disease.

The forms of α-tocopherol that meet the recommended intakes are *RRR*-α-tocopherol — the only naturally occurring form of vitamin E — and the three synthetic isomers, *RRS*-, *RSR*-, and *RSS*-α-tocopherol, which are found in nutritional supplements and fortified food.

Table 1 lists the RDA for α-tocopherol expressed in both milligrams (mg) and international units (IU).

Table 1. Recommended Dietary Allowance (RDA) for α-Tocopherol*#

Life Stage	Age	Males		Females	
		mg/day	IU/day	mg/day	IU/day
Infants (AI)	0-6 months	4	6	4	6
Infants (AI)	7-12 months	5	7.5	5	7.5
Children	1-3 years	6	9	6	9
Children	4-8 years	7	10.5	7.5	10.5
Children	9-13 years	11	16.5	11	16.5
Adolescents	14-18 years	15	22.5	15	22.5
Adults	19 years and older	15	22.5	15	22.5
Pregnancy	all ages	-	-	15	22.5
Breast-feeding	all ages	-	-	19	28.5

*These recommended intakes are limited to 2*R*-stereoisomeric forms of α-tocopherol.
#One mg of 2*R*-α-tocopherol is equivalent to 1.5 IU, and one IU is equivalent to 0.67 mg of 2*R*-α-tocopherol.

Disease Prevention

Age-related deterioration of immune function

The natural age-related decline of the immune function is accompanied by an increased susceptibility to infections, a poorer response to immunization, and higher risks of developing cancers and autoimmune diseases. α-Tocopherol has been shown to enhance specifically the T cell-mediated immune response that declines with advancing age (reviewed in 28). T cell impaired response has been partly associated with a reduced capacity of naïve T cells to be activated during antigen presentation, and to produce interleukin-2 (IL-2) and proliferate as a result (6). However, very few studies have addressed the potential association between α-tocopherol and immune function in humans (28). In a small intervention study in older adults (mean age, 70 years), supplementation with 200 mg/day of *all-rac*-α-tocopherol (equivalent to 100 mg of *RRR*-α-tocopherol) for three months significantly improved natural killer (NK) cytotoxic activity, neutrophil chemotaxis, phagocytic response, and enhanced mitogen-induced lymphocyte proliferation and interleukin-2 (IL-2) production compared to baseline (29). In an earlier trial, daily supplementation of healthy older adults (≥65 years of age) with 200 mg of *all-rac*-α-tocopherol for 235 days also improved T lymphocyte-mediated immunity — as measured with the delayed-type hypersensitivity (DTH) skin test — and increased the production of antibodies in response to hepatitis B and tetanus vaccines (30).

Lower α-tocopherol doses failed to improve the DTH response compared to a placebo in another study in healthy participants (ages, 65-80 years) (31). A randomized, placebo-controlled trial in 617 nursing home residents (≥65 years of age) reported that daily supplementation with 200 IU of synthetic α-tocopherol (90 mg of *RRR*-α-tocopherol) for one year significantly lowered the risk of contracting upper respiratory tract infections, especially the common cold, but had no effect on lower respiratory tract (lung) infections (32). More research is needed to examine whether supplemental vitamin E might enhance immune function and reduce risk of infection in older adults.

Cardiovascular disease

Primary prevention: in healthy adults

Observational studies: Results of several large observational studies in both men and women have suggested an inverse relationship between vitamin E consumption and risk of myocardial infarction or death from heart disease. Each study had a prospective design that measured vitamin E intake in generally healthy people who were followed over a period of time to determine the onset of cardiovascular events and analyze the association between the exposure and the outcome(s). In two of the studies, individuals who consumed more than 7 mg/day of dietary α-tocopherol were 35% less likely to die from heart disease than those who consumed less than 3-5 mg/day of α-tocopherol (33, 34). Two other large studies observed a significantly reduced risk of heart disease only in women and men who consumed at least 100 IU (67 mg)/day of supplemental *RRR*-α-tocopherol (35, 36).

Intervention studies: A randomized, placebo-controlled, intervention trial in 39,876 women (aged ≥45 years) participating in the Women's Health Study (WHS) found that supplementation with 600 IU (400 mg) of *RRR*-α-tocopherol every other day for 10 years resulted in a 34% reduction in nonfatal myocardial infarction and a 49% reduction in cardiovascular-related deaths but only in women aged at least 65 years at baseline (representing 10% of study participants) (37). Further analyses of WHS data showed that women in the vitamin E arm of the study experienced a 21% reduction in risk of venous thromboembolism (VTE) compared to placebo: the reduction was of 12% in women younger than 55 years old, 26% in women aged 65 years and older, and 44% in women with a history of VTE (38, 39). Another large randomized controlled trial — the Physicians' Health Study II (PHSII) — conducted in healthy middle-aged men found no significant effect of 400 IU of synthetic α-tocopherol (180 mg of *RRR*-α-tocopherol), given every other day for eight years, on the risk of major cardiovascular events in the entire cohort and in subgroup analyses (40). Besides, concerns were raised regarding a possible harmful effect of high-dose vitamin E supplementation on the risk of hemorrhagic stroke in this cohort (40).

Secondary prevention: in individuals with or at risk of cardiovascular disease

Conventional risk factors for cardiovascular disease (CVD) include cigarette smoking, physical inactivity, hypertension, dyslipidemia, and being overweight or obese. Other factors such as oxidative stress and inflammation are also thought to contribute to increasing CVD risk, especially in patients with chronic conditions like type 2 diabetes mellitus and chronic kidney disease. Although trials do not appear to support any cardiovascular benefit in healthy middle-aged and older subjects, vitamin E supplementation might help improve cardiovascular health and/or lower the risk of CVD in specific, higher risk subjects.

Observational studies: The presence of atherosclerotic plaques in arterial walls is one of the hallmarks of cardiovascular disease. Plaque rupture that causes blood clot formation is the usual cause of myocardial and cerebrovascular infarctions. The cross-sectional Asymptomatic Carotid Atherosclerosis Disease In Manfredonia (ACADIM) study in 640 at-risk individuals reported an inverse association between carotid intima-media thickness (CIMT) — a marker of atherosclerosis — and circulating concentrations of antioxidants, including vitamin E (41). However, other observational studies found no association between plasma vitamin E concentrations and CIMT (reviewed in 42).

Intervention studies: A small randomized controlled study assessing the effect of lipid-lowering drugs in men who had previously undergone a coronary artery bypass surgery found that the use of at least 100 IU/day (compared to less than 100 IU/day) of supplemental α-tocopherol (45 mg of *RRR*-α-tocopherol) was associated with reduced CIMT progression over a two-year period but only among participants in the placebo arm of the study (i.e., those who did not receive lipid-lowering drugs) (43). However, a recent meta-analysis of seven small placebo-controlled trials found little evidence that vitamin E supplementation may improve flow-mediated vascular dilation (FMD) of the brachial artery, a marker of vascular endothelial health that is adversely affected by CVD risk factors (44). In the Cambridge Heart AntiOxidant Study (CHAOS), a randomized, placebo-controlled intervention trial in 2,002 patients with coronary heart disease, daily supplementation with either 400 IU or 800 IU of synthetic α-tocopherol (180 mg or 360 mg of *RRR*-α-tocopherol) for a median 18 months dramatically reduced the occurrence of nonfatal myocardial infarctions by 77%. However, vitamin E supplementation did not significantly reduce total or cardiovascular-related deaths (45).

Another small trial in patients with renal failure — the Secondary Prevention with Antioxidants of cardiovascular disease in End-stage renal disease (SPACE) — found that supplementation with 800 IU (536 mg)/day of *RRR*-α-tocopherol for an average of 1.4 years significantly reduced the risk of myocardial infarction compared to placebo (46). A more recent randomized controlled study suggested that vitamin E supplementation may benefit a subgroup of patients with type 2 diabetes mellitus. The multicenter study by Milman et al. (47) was conducted in 1,434 type 2 diabetics (≥55 years old) carrying a specific variant of the haptoglobin protein (Hp), Hp2-2, which has a lower efficacy to bind and remove pro-oxidant, free hemoglobin from plasma, compared to Hp1-1 and Hp1-2 variants. The daily supplementation with 400 IU (268 mg) of *RRR*-α-tocopherol for 18 months resulted in a lower risk of myocardial infarction compared to placebo (47).

Other larger intervention trials conducted in cigarette smokers (the Alpha-Tocopherol, Beta-Carotene cancer prevention [ATBC] study (48)), in individuals at-risk of CVD (the Heart Outcomes Prevention Evaluation [HOPE]-The Ongoing Outcomes [HOPE-TOO study] (49)), or in patients who have suffered a myocardial infarction (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico-GISSI-prevenzione trial (50)) failed to find significant CVD risk reductions with α-tocopherol supplementation. Besides, potentially harmful effects of supplemental vitamin E were reported on the risk of hemorrhagic stroke in the ATBC trial and on the risk of heart failure in the HOPE and GISSI trials (see Safety) (48-50).

Cancer

Oxidative damage to DNA by free radicals can lead to mutations that may contribute to causing cancer (51). Because of its ability to neutralize free radicals, vitamin E has been suggested to possess anticancer activity by protecting cells against oxidative damage. Yet, several large prospective cohort studies have failed to find significant associations between vitamin E intake and the incidence of lung or breast cancer (2). More recently, the VITamins And Lifestyle (VITAL) study prospectively assessed the association between long-term use of supplemental vitamins (10-year intake) and the risk of lung cancer in a cohort of 77,126 men and women (52). No relationships were reported between intake of multivitamins, vitamin C, vitamin E, or folate and the risk of lung cancer. However, the use of supplemental vitamin E in current but not in former smokers was associated with an 11% increased risk of lung cancer for every 100 mg/day increase, and intakes greater than 215 mg/day were specifically linked to a 29% increase in risk for non-small cell lung cancer (52).

To date, most clinical trials have failed to find any beneficial effects of vitamin E supplementation on the risk of various cancers. A randomized, placebo-controlled trial (RCT) in 39,876 women participating in the Women's Health Study found that supplementation with 600 IU (400 mg) of *RRR*-α-tocopherol every other day for 10 years had no effect on overall cancer incidence, tissue-specific cancer incidence, or cancer-related deaths (37). Yet, the results of a few large randomized controlled trials have suggested that vitamin E supplementation might affect the risk of prostate cancer. The Alpha-Tocopherol, Beta-Carotene cancer (ATBC) prevention study was a four-arm, randomized, double-blind, placebo-controlled trial designed to investigate the effect of α-tocopherol supplementation on lung cancer development in 29,133 male smokers. The study found a 32% reduction in the incidence of prostate cancer in participants given daily supplements of 50 mg of synthetic α-tocopherol (equivalent to 25 mg of *RRR*-α-tocopherol) alone or in combination with β-carotene compared to those given β-carotene alone or a placebo (53). However, no differences in the incidence of prostate cancer were found between α-tocopherol recipients and nonrecipients during the 18-year post-intervention period (54). In the Physicians' Health Study II (PHS II), which followed 14,641 healthy men aged 50 years and older, supplementation with 400 IU of synthetic vitamin E (equivalent to 180 mg of *RRR*-α-tocopherol) every other day for eight years had no effect on the risk of prostate cancer, other site-specific cancers, or total cancer (55). The supplementation of vitamin E (equivalent to 180 mg/day of *RRR*-α-tocopherol), alone or in combination with selenium, in the multicenter, randomized, placebo-controlled SELECT trial (SELenium and vitamin E Cancer prevention Trial) was halted because there was no evidence of benefit in preventing prostate cancer in 35,533 healthy men aged 50 years and older (56). After a median of seven years' follow-up, the risk of prostate cancer was found to be significantly increased by 17% in participants supplemented with vitamin E alone during the trial period — but not when vitamin E was combined with selenium — compared to placebo (57). A study of cases versus subcohort individuals drawn from the SELECT study assessed the effect of vitamin E and/or selenium supplementation on prostate cancer risk in relation to the selenium status of participants at baseline (58). Supplemental selenium with or without vitamin E was associated with a significant increase in the risk of advanced prostate cancer in individuals with higher versus lower selenium status. In addition, the risks of total and advanced prostate cancer were significantly elevated with vitamin E supplementation in subjects with low versus high selenium status (58). Recent investigations have suggested that sequence variations (polymorphisms) in vitamin E-related genes and genes coding for antioxidant enzymes, including selenoproteins, might modify the impact of high-dose vitamin E and selenium on the risk of prostate cancer (59-61).

Cataracts

Age-related cataracts appear to be the result of protein oxidation in the lens of the eye; antioxidants like α-tocopherol may protect the lens against oxidative damage from reactive oxygen species. In a recent cross-sectional study, vitamin E concentrations were found to be significantly lower in the lens and blood of subjects with age-related nuclear, but not cortical, cataracts when compared with an age-matched control group (62). However, earlier studies reported higher vitamin E concentrations in the lenses and blood of patients with cataracts (63, 64).

The results of several observational studies that examined the association between vitamin E consumption and the incidence or severity of cataracts are also mixed. Some reported that increased vitamin E intake protected against cataract development, while others found no association (65). Yet, a meta-analysis of eight studies, including 15,021 participants, found a 17% reduction in the risk of age-related cataract in subjects in the highest versus lowest quantile of dietary vitamin E intake (66). A recent prospective cohort study of 31,120 Swedish men followed for a mean of 8.4 years observed a greater risk of developing cataract in occasional and regular users of high-dose (about 100 mg/day) vitamin E supplements only, when compared with non-supplement users (67). However, the use of supplemental high-dose vitamin E with additional supplements or the use of low-dose vitamin E-containing multivitamin supplements was not found to be associated with an elevated cataract risk. A meta-analysis based on data from over 350,000 participants in 10 studies — including the above-cited study by Zheng Selin et al. (67) — found no association between supplemental vitamin E and risk of cataract (66).

In clinical settings, the supplementation of high-dose vitamin E — alone or in addition to other supplements — was found to be safe, yet the benefits regarding cataract risk or progression were limited. An early intervention trial found that a daily supplement of 50 mg of synthetic α-tocopherol (equivalent to 25 mg of *RRR*-α-tocopherol) did not alter the incidence of cataract surgery in male smokers (68). A randomized, placebo-controlled intervention trial in 4,629 men and women found that a daily antioxidant supplement containing 500 mg of vitamin C, 400 IU of *all-rac*-α-tocopheryl acetate (equivalent to 180 mg of *RRR*-α-tocopherol), and 15 mg of β-carotene did not affect development and progression of age-related cataracts over a seven-year period (69). Similarly, a four-armed, randomized, placebo-controlled study of 11,267 men from the Selenium and Vitamin E Cancer prevention trial (SELECT) failed to observe a reduction in cataract incidence with 400 IU/day of supplemental *all-rac*-α-tocopheryl acetate (180 mg/day of *RRR*-α-tocopherol), alone or in combination with selenium (200 µg/day), during a mean 5.6 years of follow-up (70). Daily antioxidant supplementation with 500 mg of vitamin C, 400 IU (268 mg) of *RRR*-α-tocopherol, and 15 mg of β-carotene did not limit the progression of cataract in a five-year intervention trial (71). Another four-year randomized, placebo-controlled trial reported that supplements containing 500 IU/day (335 mg/day) of *RRR*-α-tocopherol did not reduce the incidence or progression of cataract in older adults (72). Current available data from clinical trials do not support a preventative effect of vitamin E on cataracts.

Disease Treatment

Age-related macular degeneration

A recent pooled analysis of four randomized controlled trials in 62,520 subjects found that supplemental vitamin E or β-carotene did not reduce the risk of developing age-related macular degeneration (AMD), a multifactorial disease affecting the central area of the retina (73). However, a review of currently available data suggested that supplements of antioxidants plus zinc may reduce the progression of AMD and vision loss in affected individuals (74). The main evidence came from the Age-Related Eye Disease Study (AREDS). In this clinical trial, participants with borderline to advanced age-related macular degeneration (AMD) were randomized to receive (1) placebo; (2) antioxidant vitamins (15 mg/day of β-carotene, 500 mg/day of ascorbic acid, and 400 IU/day of *all-rac*-α-tocopheryl acetate); (3) zinc (80 mg/day) and copper (2 mg/day); or (4) both antioxidant vitamins and zinc and copper (75). The five-year results indicated that the risk of developing advanced AMD was significantly reduced in those taking zinc with or without antioxidant vitamins. Antioxidant vitamins alone failed to prevent the progression to advanced AMD, even in individuals at higher risk. It was concluded from this study that a combination of antioxidant vitamins and minerals may benefit people with intermediate AMD or advanced AMD in one eye (74, 76).

Type 2 diabetes mellitus

Oxidative stress contributes to the progression of type 2 diabetes mellitus and causes damage to many organs and tissues, including the pancreas, brain, eyes, peripheral nerves, and kidneys. Evidence from animal studies suggests that vitamin E supplementation could mitigate the role of oxidative damage in the occurrence of diabetes complications (reviewed in 77). In the Alpha-Tocopherol Beta-Carotene cancer prevention (ATBC) trial in male smokers, supplementation with 50 mg/day of synthetic α-tocopherol (25 mg/day of *RRR*-α-tocopherol) had no effect on the risk of incident type 2 diabetes mellitus during the 19-year post-intervention follow-up. Likewise, supplemental vitamin E intake during the trial made no difference on the incidence of macrovascular complications or mortality in participants with established type 2 diabetes (78). In addition, a meta-analysis of 14 heterogeneous randomized controlled trials, including 714 type 2 diabetic individuals, found that supplementation with vitamin E (200-1,800 IU/day for 6-27 weeks) had no effect on markers of glycemic control, including glycated hemoglobin A1c (HbA1c) level and measures of fasting glucose and fasting insulin concentrations (79). Further subgroup analyses indicated that higher doses of vitamin E (>400 IU/day) supplemented for longer periods (>12 weeks) significantly reduced HbA1c level and fasting insulin concentration, suggesting that vitamin E could possibly enhance insulin action and glucose disposal in type 2 diabetic individuals (79). Another recent meta-analysis of randomized controlled trials found that endothelial function in normal-weight and overweight — but not obese — patients with type 2 diabetes was significantly improved by supplementation with vitamin E and/or vitamin C (80). Although there is reason to suspect that vitamin E supplementation may have utility in the management of type 2 diabetes, evidence for benefit from large, well-controlled clinical trials is still lacking.

Fatty liver diseases

The increasing incidence of nonalcoholic fatty liver disease (NAFLD) in children and adults in industrialized countries is mainly attributed to the ongoing epidemic of obesity and type 2 diabetes mellitus. NAFLD results from the abnormal accumulation of fat (steatosis) in the liver in the absence of heavy alcohol consumption. Although the condition is considered to be largely benign, NAFLD can progress to a more severe disease called nonalcoholic steatohepatitis (NASH) with increased risks of cirrhosis, hepatocellular carcinoma (liver cancer), and cardiovascular disease (81). Oxidative stress is thought to be one of the possible mechanisms responsible for prompting inflammatory processes that can lead to the progression of NAFLD to NASH.

There is currently no established treatment for NAFLD and NASH other than interventions that encourage lifestyle changes and the use of medicines to control or treat metabolic disorders (82). In the multicenter PIVENS (PIoglitazone versus Vitamin E versus placebo for the treatment of Nonalcoholic Steatohepatitis) trial, 247 nondiabetic subjects with NASH were randomized to receive 30 mg/day of pioglitazone (an insulin-sensitizing drug), 800 IU/day (536 mg/day) of *RRR*-α-tocopherol, or a placebo for 96 weeks (83). Only vitamin E supplementation significantly increased the overall rate of improvement in histological abnormalities that characterize NASH on liver biopsies (i.e., hepatocellular ballooning, steatosis, and lobular inflammation) (84). Both active treatments improved some markers of liver function (i.e., alanine aminotransferase and aspartate aminotransferase) (84). Yet, results from another two-year, randomized controlled trial — called TONIC for Treatment Of Nonalcoholic fatty liver disease In Children — in 173 children (ages, 8-17 years) with NAFLD failed to observe any significant reduction in blood concentrations of alanine and aspartate aminotransferases either with supplemental vitamin E (536 mg/day of *RRR*-α-tocopherol) or with metformin (an anti-diabetic drug; 1,000 mg/day) compared to placebo (85). However, vitamin E supplementation significantly improved the overall disease activity score — used to quantify the severity of the disease. In addition, a recent meta-analysis of another six trials found that vitamin E significantly lowered circulating aminotransferase concentrations in NAFLD and NASH patients, suggesting liver function improvements (86). Finally, in a small nonrandomized, unblinded, controlled study in 42 obese children (mean age, 8 years) with NAFLD, lifestyle recommendations combined with 600 mg/day of supplemental *RRR*-α-tocopheryl acetate for six months reduced markers of oxidative stress and liver dysfunction and improved insulin sensitivity and the profile of lipid in the blood, when compared to baseline. No such changes in markers of oxidative stress, liver function, and glucose utilization were reported in the lifestyle intervention only group (87). Further randomized and well-controlled studies are needed to confirm these preliminary findings.

Cognitive deterioration and Alzheimer's disease

Mitochondrial dysfunction and oxidative stress are thought to contribute to the onset and/or progression of several neurodegenerative diseases, especially Alzheimer's disease (AD) (88). The progressive degeneration of neuronal cells that accompanies the decline of memory and other cognitive functions in subjects with Alzheimer's disease is associated with an intracellular aggregation of Tau fibrils, an extraneuronal accumulation of β-amyloid peptides into senile plaques, and an oxidation-reduction (redox) imbalance of complex etiology. In the brain of patients with mild cognitive impairment (MCI) and those with AD, the level of markers of oxidative damage to DNA, proteins, and lipids is increased, while the expression and activities of glutathione and antioxidant enzymes are reduced (reviewed in 88). In addition, a recent meta-analysis reported that circulating concentrations of vitamins, including vitamin A, vitamin C, and vitamin E, were significantly lower in AD patients than in cognitively healthy individuals (89). Other studies have documented low concentrations of vitamin E in cerebrospinal fluid of cognitively impaired patients (reviewed in 90).

Because a reduction in oxidative stress may help maintain cognitive status and/or prevent deterioration, the effects of vitamin E supplementation have been assessed in a few intervention studies. An early multicenter, randomized, placebo-controlled study in individuals with AD of moderate severity found that supplementation with 2,000 IU/day of *all-rac*-α-tocopherol (equivalent to 900 mg/day of *RRR*-α-tocopherol) for two years significantly delayed cognitive decline, slowed disease progression, and increased median survival (91). However, a placebo-controlled trial in 769 patients with MCI found that the same dosage of vitamin E did not affect the probability of progression from MCI to AD over a three-year period (92). In another double-blind, placebo-controlled trial, an improvement in cognitive performance — measured by the Mini Mental State Examination (MMSE) scoring system — was reported in AD patients randomized to receive 800 IU/day of *all-rac*-α-tocopherol (360 mg/day of *RRR*-α-tocopherol) for six months only when the treatment effectively reduced oxidative stress (as assessed by the measure of total glutathione and markers of lipid peroxidation in the blood) (93). Conversely, a failure to reduce oxidative stress resulted in supplemental vitamin E being more detrimental to the cognitive function of AD patients than placebo. In the most recent multicenter, randomized, double-blind, placebo-controlled study, supplemental vitamin E (2,000 IU/day; form of vitamin E not mentioned in the publication) for over two years significantly delayed functional decline — determined by the (in)ability to perform basic activities of daily living — and reduced the annual mortality rate in mild and moderate AD patients (94). Yet, vitamin E failed to affect cognitive performance measured with MMSE scores and other cognitive ability tests.

While there is currently little evidence to suggest that long-term supplementation of vitamin E provides any cognitive benefits in healthy older adults (95), additional research needs to confirm whether vitamin E supplementation could benefit the management of patients with mild-to-moderate cognitive impairments.

Sources

Food sources

Major sources of α-tocopherol in the American diet include vegetable oils (olive, sunflower, and safflower oils), nuts, whole grains, and green leafy vegetables. All eight forms of vitamin E (α-, β-, γ-, and δ-tocopherols and α-, β-, γ-, and δ-tocotrienols) occur naturally in mostly plant-based foods but in varying amounts. **Table 2** lists the content of α-tocopherol and γ-tocopherol (in milligrams) in some rich sources of vitamin E. For more information on the vitamin E content of foods, search USDA's FoodData Central.

Table 2. Some Food Sources of Vitamin E

Food	Serving	α-Tocopherol (mg)	γ-Tocopherol (mg)
Sunflower oil	1 tablespoon	5.6	0.6
Safflower oil	1 tablespoon	4.6	-
Grapeseed oil	1 tablespoon	3.9	-
Canola oil	1 tablespoon	2.4	3.8
Corn oil	1 tablespoon	1.9	-
Olive oil	1 tablespoon	1.9	0.1
Soybean oil	1 tablespoon	1.1	8.7
Sunflower seed kernels, dry roasted	1 ounce	7.4	0
Almonds	1 ounce	7.3	0.2
Hazelnuts	1 ounce	4.3	0
Peanuts	1 ounce	2.4	2.4
Pecans	1 ounce	0.4	6.9
Peanut butter, smooth	2 tablespoons	3.2	-
Tomato sauce, canned	1 cup	3.5	0.2
Cranberry juice	1 cup (8 fl oz)	3.0	-
Apricots, dried	½ cup (halves)	2.8	0
Avocado (California)	1 fruit	2.7	0.4
Fish, rainbow trout, cooked, dry-heat	3 ounces	2.4	0
Spinach, cooked, boiled	½ cup	1.9	-
Asparagus, canned	½ cup	1.5	-
Swiss chard, cooked, boiled	½ cup (chopped)	1.6	-
Broccoli, cooked, boiled	½ cup (chopped)	1.1	-
Blackberries, raw	½ cup	0.8	0.3

In the US, the average intake of α-tocopherol from food (including enriched and fortified sources) for adults (≥19 years of age) is 7.2 mg/day (25); this level is well below the RDA of 15 mg/day of α-tocopherol (see **Table 1**). While it appears feasible for individuals to meet the RDA from food only, Americans would have to depart from their current dietary practices and include greater intakes of nuts, seeds, fruit, and vegetables without increasing fat intake above recommended levels (96).

Supplements

RRR-α-tocopherol is the only stereoisomeric form of α-tocopherol found in unfortified foods. The same is not always true for nutritional supplements. Vitamin E supplements generally contain 100 IU to 1,000 IU of α-tocopherol. Supplements made from entirely natural sources contain only *RRR*-α-tocopherol (wrongly labeled *d*-α-tocopherol). *RRR*-α-tocopherol is the most bioavailable form of α-tocopherol in the body. Synthetic α-tocopherol, which is often found in fortified food and nutritional supplements and usually labeled *all-rac*-α-tocopherol or *dl*-α-tocopherol, include all eight possible stereoisomers of α-tocopherol (see Function). Because half of the isomers present as a mixture in synthetic α-tocopherol are not usable by the body, synthetic α-tocopherol is less bioavailable than natural α-tocopherol (see **Figure 1**). To calculate the amount (in milligrams) of α-tocopherol bioavailable in a supplement, the conversion factors are as follows:

- Natural vitamin E (*RRR*-α-tocopherol) containing supplements:
  IU of *RRR*-α-tocopherol x 0.67 = mg of *RRR*-α-tocopherol
  Example: 100 IU of natural vitamin E provides 67 mg of *RRR*-α-tocopherol
- Synthetic vitamin E (*all-rac*-α-tocopherol) containing supplements:
  IU of *all-rac*-α-tocopherol x 0.45 = mg of *RRR*-α-tocopherol
  Example: 100 IU of synthetic vitamin E provides 45 mg of 2*R*-α-tocopherol

In addition, vitamin E-fortified foods often contain synthetic α-tocopherol, and amounts of vitamin E are provided as a percentage of the daily value (DV) of 30 IU (approximately 20 mg of *RRR*-α-tocopherol).

α-Tocopheryl esters

α-Tocopheryl succinate and α-tocopheryl acetate are the main esterified forms of vitamin E in nutritional supplements. Tocopherol esters are more resistant to oxidation during storage than unesterified tocopherols (1). When taken orally, the succinate or acetate moieties are removed from α-tocopherol in the intestine. The bioavailability of α-tocopherol from α-tocopheryl succinate and α-tocopheryl acetate is equivalent to that of free α-tocopherol (97). Hence, the conversion factors used to determine the amount of bioavailable α-tocopherol provided by α-tocopheryl succinate and α-tocopheryl acetate are the same as those used for α-tocopherol (see above) (2). Cell culture studies indicated that the vitamin E ester, α-tocopheryl succinate, could inhibit proliferation and induce apoptosis in a number of cancer cell lines (12). Limited data from animal models of cancer found that α-tocopheryl succinate administered by injection inhibited tumor growth (98). There is currently no evidence in humans that taking oral α-tocopheryl succinate supplements delivers α-tocopheryl succinate to tissues. Of note, current research investigates nanomedicines to increase α-tocopheryl succinate bioavailability before exploring putative benefits in clinical settings (98).

α-Tocopheryl nicotinate is another α-tocopherol ester formed from synthetic α-tocopherol and nicotinic acid (niacin). While α-tocopheryl nicotinate can be prescribed as a lipid-lowering agent in Europe and Japan, it is marketed as a supplement only in the US (99).

α-Tocopheryl phosphates (Ester-E®)

There is currently no published evidence that supplements containing α-tocopheryl phosphates are more efficiently absorbed or have greater bioavailability in humans than those containing α-tocopherol (99).

Other supplemental forms

Supplements containing γ-tocopherol, mixed tocopherols, or tocotrienols are also commercially available (99). The amounts of α- and γ-tocopherol in mixed tocopherol supplements vary, so it is important to read the label to determine the amount of each tocopherol form present in a capsule.

Safety

Toxicity

Few side effects have been noted in adults taking supplements of less than 2,000 mg of α-tocopherol daily (either natural or synthetic vitamin E). However, most studies assessing safety issues or toxicity of α-tocopherol supplementation have lasted only a few weeks to a few months, and side effects associated with long-term α-tocopherol supplementation have not been adequately studied. The most worrisome possibility is that of impaired blood clotting, which increases the likelihood of hemorrhage in some individuals. A meta-analysis of randomized controlled trials found that daily vitamin E supplementation — equivalent to 25 to 536 mg/day of *RRR*-α-tocopherol — for several years resulted in a significant, 10% reduction in the risk of ischemic stroke (five trials, 91,393 participants) and a nonsignificant trend towards an increased risk of hemorrhagic stroke (five trials, 100,748 participants) (100).

A tolerable upper intake level (UL) for any form of supplemental α-tocopherol (all possible stereoisomers) has been established by the Food and Nutrition Board of the Institute of Medicine to avoid the potential risk of bleeding (**Table 3**). Specifically, the UL of 1,000 mg/day of α-tocopherol in any supplemental form (equivalent to 1,500 IU/day of *RRR*-α-tocopherol or 1,100 IU/day of *all-rac*-α-tocopherol) corresponds to the highest dose unlikely to result in hemorrhage in almost all adults (2). Although only certain isomers of α-tocopherol are retained in the circulation, all forms are absorbed and metabolized by the liver. Hence, the rationale for a UL that refers to all stereoisomers of α-tocopherol is based on the fact that any form of α-tocopherol (natural or synthetic) can be absorbed and thus be potentially harmful.

Table 3. Tolerable Upper Intake Level (UL) for α-Tocopherol*

Age Group	mg/day#
Infants 0-12 months	Not possible to establish##
Children 1-3 years	200
Children 4-8 years	300
Children 9-13 years	600
Adolescents 14-18 years	800
Adults 19 years and older	1,000

*The UL for α-tocopherol applies to all stereoisomers of α-tocopherol (natural and synthetic) found in supplements and fortified food.
#Of note, mg-to-IU conversion factors are such that the UL in IU for synthetic tocopherol (*all-rac*-α-tocopherol) is 1.10 times the UL in mg, and the UL in IU for natural tocopherol (*RRR*-α-tocopherol) is 1.50 times the UL in mg. Hence, the UL amount of 1,000 mg for adults corresponds to 1,100 IU of synthetic tocopherol or 1,500 IU of natural tocopherol.
##Source of intake should be from foods or formula only.

Some physicians recommend discontinuing high-dose vitamin E supplementation two to four weeks before elective surgery — including dental procedures — to decrease the risk of hemorrhage (99).

Because dietary vitamin E is essential to prevent vitamin E deficiency in the newborn, vitamin E must be supplied in parenteral nutrition solutions in infants who cannot be given enteral feeding, such as prematurely born infants. Yet, preterm infants appear to be especially vulnerable to adverse effects of α-tocopherol supplementation, and supplemental vitamin E should be administered only under controlled supervision by a pediatrician (101).

Finally, the results of only one randomized controlled trial in 601 patients with common forms of retinitis pigmentosa (RP) indicated that supplementation with 400 IU/day of synthetic vitamin E (equivalent to 180 mg/day of *RRR*-α-tocopherol) modestly but significantly accelerated the loss of retinal function compared to placebo (22). Patients with common forms of RP should therefore avoid taking high-dose vitamin E supplements if they are not deficient in vitamin E (see Deficiency).

Does vitamin E supplementation increase the risk of all-cause mortality?

A prospective observational study in over 4,000 participants of the Framingham Heart Study and the Framingham Offspring Study — with or without preexisting cardiovascular disease — found no statistically significant association between vitamin E supplement intake and cardiovascular or all-cause mortality after a 10-year follow-up period (102). However, in addition to reports of increased risk of hemorrhage and heart failure with supplemental vitamin E in several randomized controlled studies (see Cardiovascular disease), a meta-analysis by Miller et al. (103) suggested an increased risk of death with the use of large doses of vitamin E, yet lower than the UL. Specifically, this meta-analysis combined the results of 19 clinical trials of vitamin E supplementation that mostly focused on secondary prevention and, as such, included subjects with pre-existing conditions including heart disease, end-stage renal failure, and Alzheimer's disease. The study found that daily supplementation with at least 400 IU of synthetic vitamin E (equivalent to 180 mg of *RRR*-α-tocopherol) resulted in a 4% increase in risk of death from any cause compared to placebo (103). However, further dose-response analysis and adjustment for intake of other vitamin and mineral supplements indicated that all-cause mortality risk was significantly increased by 7% only at a dose of 2,000 IU/day, which is notably higher than the UL for adults (1,100 IU/day of synthetic tocopherol or 1,500 IU/day of natural tocopherol; see **Table 3**). Additionally, a more recent meta-analysis of 46 randomized trials, including 171,244 participants, found that supplemental vitamin E, singly or in combination with other antioxidants, did not significantly alter the risk of all-cause mortality (104). At present, there is no convincing evidence that vitamin E supplementation below the UL increases the risk of death from cardiovascular disease or other causes, especially in generally healthy subjects. Yet, individuals with pre-existing conditions may be at increased risk of serious adverse effects (including death) if one considers the possibility that large doses of supplemental vitamin E might interfere with medications, and possibly lower their efficacy or increase their toxicity (1).

Nutrient interactions

Large doses of vitamin E may inhibit vitamin K-dependent carboxylase activity and interfere with the coagulation cascade (see the article on Vitamin K) (19). Hence, the use of vitamin E supplements may increase the risk of bleeding in individuals taking anticoagulant drugs (blood thinners), such as heparin and the vitamin K antagonist, warfarin (Coumadin); antiplatelet drugs, such as clopidogrel (Plavix), ticlopidine (Ticlid), tirofiban (Aggrastat), and dipyridamole (Aggrenox); and non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, ibuprofen, and others. In addition, individuals who may be vitamin K deficient due to liver failure, those with a propensity to bleed (e.g., bleeding peptic ulcers), and those with inherited bleeding disorders (e.g., hemophilia) or a history of hemorrhagic stroke, should not take α-tocopherol supplements without close medical supervision because of the increased risk of hemorrhage (20, 99). Finally, it cannot be excluded that vitamin E would potentiate the antithrombotic activity of supplemental fish oils and herbal products, such as garlic, curcumin, or Ginkgo biloba (99).

Drug interactions

A number of cholesterol-lowering medications (like cholestyramine and colestipol), as well as orlistat, sucralfate, mineral oil, and the fat substitute, olestra, which interfere with fat absorption, may theoretically decrease the absorption of fat-soluble vitamins, including vitamin E. The anticonvulsant drugs phenobarbital, phenytoin (Dilantin), and carbamazepine (Tegretol), may also lower plasma vitamin E concentrations in individuals with epilepsy (105).

Antioxidants and statins (3-hydroxy-3-methylglutary-coenzyme A reductase inhibitors)

A three-year randomized controlled trial in 160 patients with coronary heart disease (CHD) and low high-density-lipoprotein (HDL) levels found that a combination of simvastatin (Zocor) and niacin increased the HDL2 subfraction level (considered the most cardioprotective), inhibited the progression of coronary artery stenosis (narrowing), and decreased the frequency of cardiovascular events, such as myocardial infarction and stroke (106). Surprisingly, when an antioxidant combination of 1,000 mg of vitamin C, 800 IU (536 mg) of *RRR*-α-tocopherol, 100 µg of selenium, and 25 mg of β-carotene daily, was taken with the simvastatin-niacin combination, the protective effects were diminished. However, in a much larger randomized controlled trial of simvastatin and an antioxidant combination of 600 mg of *all-rac*-α-tocopherol (297 mg of *RRR*-α-tocopherol), 250 mg of vitamin C, and 20 mg of β-carotene daily in more than 20,000 men and women with CHD or diabetes, the antioxidant combination did not adversely affect the cardioprotective effects of simvastatin therapy over a five-year period (107). These contradictory findings indicate that further research is needed on potential interactions between antioxidant supplementation and cholesterol-lowering agents like statins.

Linus Pauling Institute Recommendation

The Recommended Dietary Allowance (RDA) for vitamin E for adult men and women is 15 mg (22.5 IU) per day. Notably, more than 90% of individuals two years of age and older in the US do not meet the daily requirement for vitamin E from food sources alone. Therefore, LPI recommends that generally healthy adults (aged 19 years and older) take a daily multivitamin/mineral (MVM) supplement, which usually contains 30 IU of synthetic vitamin E — equivalent to 13.5 mg of *RRR*-α-tocopherol and 90% of the RDA.

Older adults (>50 years)

The Linus Pauling Institute's recommendation to take a daily multivitamin/mineral (MVM) supplement containing vitamin E is also appropriate for generally healthy older adults. MVMs typically contain 30 IU of synthetic vitamin E, covering 90% of the RDA.

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Vitamin K

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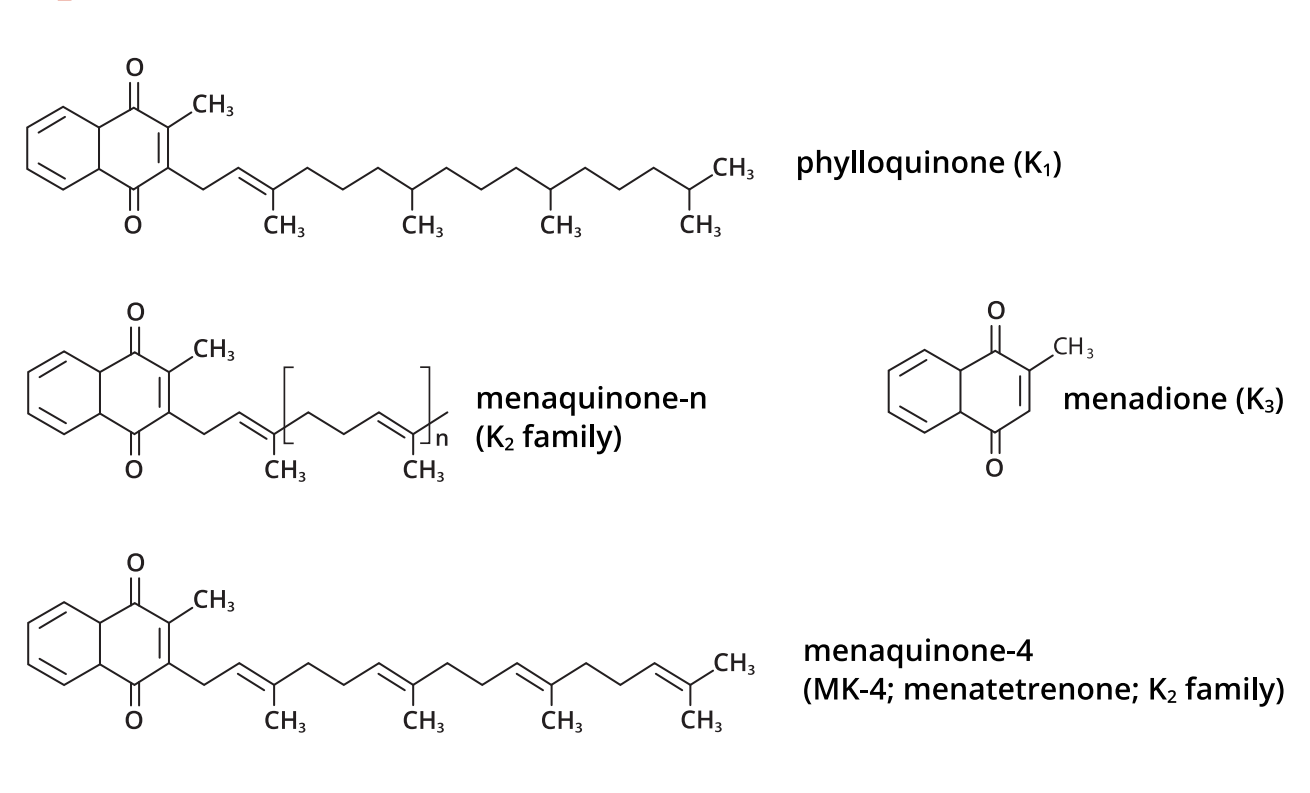
Summary

- Naturally occurring forms of vitamin K include phylloquinone (vitamin K$_1$) and a family of molecules called menaquinones (MKs or vitamin K$_2$). *(More information)*
- With limited vitamin K storage capacity, the body recycles vitamin K in the vitamin K oxidation-reduction cycle in order to reuse it multiple times. *(More information)*
- Vitamin K is the essential cofactor for the carboxylation of glutamic acid residues in many vitamin K-dependent proteins (VKDPs) that are involved in blood coagulation, bone metabolism, prevention of vessel mineralization, and regulation of various cellular functions. *(More information)*
- Vitamin K deficiency increases the risk of excessive bleeding (hemorrhage). An injection of vitamin K is recommended to protect all newborns from life-threatening bleeding within the skull. *(More information)*
- The adequate intake (AI) level for vitamin K is set at 90 μg/day for women and 120 μg/day for men. *(More information)*
- Vitamin K deficiency may impair the activity of VKDPs and increase the risk of osteoporosis and fractures. Some, but not all, observational studies have found lower vitamin K status to be associated with lower bone mineral density and higher fracture incidence. Overall, intervention trials have been inconclusive regarding the role of supplemental vitamin K (vitamin K$_1$ or vitamin K$_2$) in further reducing bone loss in otherwise calcium- and vitamin D-replete adults. *(More information)*
- Abnormal mineralization of blood vessels increases with age and is a major risk factor for cardiovascular disease. Vitamin K inadequacy may inactivate several VKDPs that inhibit the formation of calcium precipitates in vessels. There is only limited evidence of a benefit of supplemental vitamin K in the prevention of vessel calcification and cardiovascular events. *(More information)*
- While the results of a few observational studies suggest that low vitamin K status might have a role in development of osteoarthritis, randomized controlled trials are needed. *(More information)*
- Phylloquinone is found at high concentrations in green leafy vegetables and certain plant oils, while most menaquinones are usually found in cheese, animal products, and certain fermented foods. *(More information)*
- Several drugs, including vitamin K antagonists (e.g., warfarin), are known to interfere with vitamin K absorption and metabolism. *(More information)*

Vitamin K is a fat-soluble vitamin. Originally identified for its role in the process of blood clot formation ("K" is derived from the Danish word "koagulation"), vitamin K is essential for the functioning of several proteins involved in physiological processes that encompass, but are not limited to, the regulation of blood clotting (coagulation) (1). Naturally occurring forms of vitamin K include a number of vitamers known as vitamin K$_1$ and vitamin K$_2$ (**Figure 1**). Vitamin K$_1$ or phylloquinone is synthesized by plants and is the predominant form in the diet. Vitamin K$_2$ includes a range of vitamin K forms collectively referred to as menaquinones. Most menaquinones are synthesized by human intestinal microbiota and found in fermented foods and in animal products. Menaquinones differ in length from 1 to 13 repeats of 5-carbon units in the side chain of the molecules. These forms of vitamin K are designated menaquinone-n (MK-n), where n stands for the number of 5-carbon units (MK-2 to MK-13) (2, 3). Widely used in animal husbandry, the synthetic compound known as menadione (vitamin K$_3$) is a provitamin that needs to be converted to menaquinone-4 (MK-4) to be active (**Figure 1**) (4).

Figure 1. Chemical Structures of Vitamin K



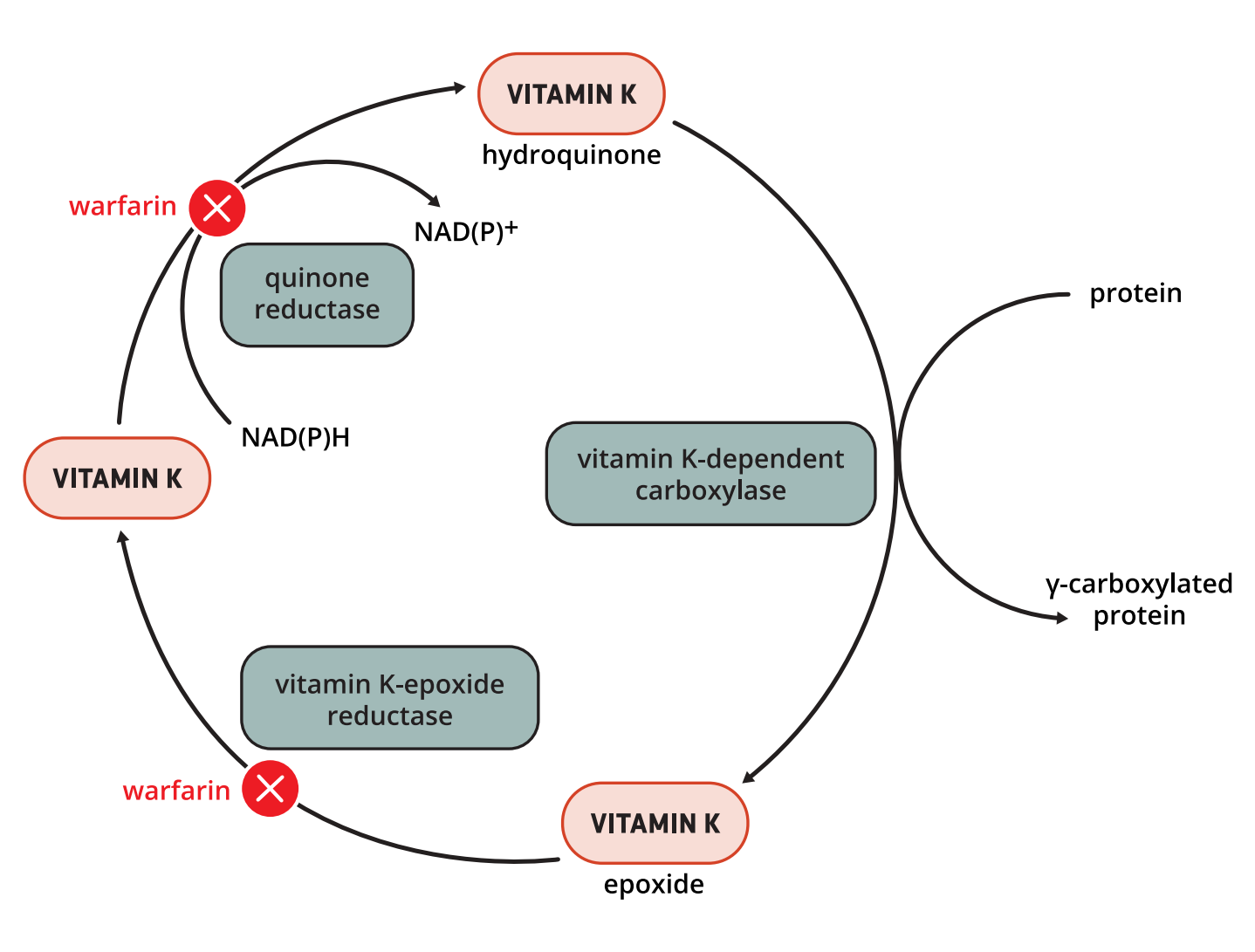
Function

Vitamin K functions as a cofactor for the enzyme, γ-glutamylcarboxylase, which catalyzes the carboxylation of the amino acid glutamic acid (Glu) to γ-carboxyglutamic acid (Gla). Vitamin K-dependent γ-carboxylation that occurs only on specific glutamic acid residues in identified vitamin K-dependent proteins (VKDP) is critical for their ability to bind calcium (5).

Vitamin K oxidation-reduction cycle

Although vitamin K is a fat-soluble vitamin, the body stores very small amounts that are rapidly depleted without regular dietary intake. Perhaps because of its limited ability to store vitamin K, the body recycles it through a process called the vitamin K-epoxide cycle (**Figure 2**). The vitamin K cycle allows a small amount of vitamin K to be reused many times for protein carboxylation, thus decreasing the dietary requirement. Briefly, vitamin K hydroquinone (reduced form) is oxidized to vitamin K epoxide (oxidized form). The reaction enables γ-glutamylcarboxylase to carboxylate selective glutamic acid residues on vitamin K-dependent proteins. The recycling of vitamin K epoxide (oxidized form) to hydroquinone (reduced form) is carried out by two reactions that reduce vitamin K epoxide (KO) to vitamin K quinone and then to vitamin K hydroquinone (KH$_2$; **Figure 2**). Additionally, the enzyme vitamin K-epoxide reductase (VKOR) catalyzes the reduction of KO to vitamin K quinone and may be involved — as well as another yet-to-defined reductase — in the production of KH2 from vitamin K quinone (6, 7). The anticoagulant drug warfarin acts as a vitamin K antagonist by inhibiting VKOR activity, hence preventing vitamin K recycling (see Coagulation).

Figure 2. The Vitamin K Cycle



The reduced form of vitamin K (hydroquinone) donates a pair of electrons to the vitamin K-dependent carboxylase (known as γ-glutamylcarboxylase), which carboxylates glutamic acid residues in specific vitamin K-dependent proteins. The resultant oxidized form of vitamin K (epoxide) is converted back to hydroquinone in a two-step reaction. The first step, which converts vitamin K epoxide to vitamin K, is catalyzed by vitamin K-epoxide reductase; the second step is catalyzed by either vitamin K-epoxide reductase or most likely by another yet-to-be-defined reductase. This pathway is inhibited by the vitamin K antagonist and anticoagulant drug, warfarin. The reduction of vitamin K to hydroquinone is also possibly catalyzed by a NAD(P)H-dependent reductase that is resistant to warfarin.

Coagulation

The ability to bind calcium ions (Ca^{2+}) is required for the activation of the several vitamin K-dependent clotting factors, or proteins, in the coagulation (clotting) cascade. The term 'coagulation cascade' refers to a series of events, each dependent on the other, that stops bleeding through clot formation. Vitamin K-dependent γ-carboxylation of specific glutamic acid residues in those proteins makes it possible for them to bind calcium. Factors II (prothrombin), VII, IX, and X make up the core of the coagulation cascade. Protein Z appears to enhance the action of thrombin (the activated form of prothrombin) by promoting its association with phospholipids in cell membranes. Protein C and protein S are anticoagulant proteins that provide control and balance in the coagulation cascade; protein Z also has an anticoagulatory function. Control mechanisms for the coagulation cascade exist since uncontrolled clotting may be as life threatening as uncontrolled bleeding. Vitamin K-dependent coagulation factors are synthesized in the liver. Consequently, severe liver disease results in lower blood levels of vitamin K-dependent clotting factors and an increased risk for uncontrolled bleeding (hemorrhage) (8).

Oral anticoagulant therapy with vitamin K antagonists

Some people are at increased risk of forming clots, which could block the flow of blood in arteries of the heart, brain, or lungs, resulting in myocardial infarction (heart attack), stroke, or pulmonary embolism, respectively. Abnormal clotting is not related to excessive vitamin K intake, and there is no known toxicity associated with vitamin K$_1$ or vitamin K$_2$ (see Toxicity). Some oral anticoagulants, such as warfarin (Jantoven, formerly known as Coumadin), inhibit coagulation by antagonizing the action of vitamin K. Warfarin prevents the recycling of vitamin K by blocking VKOR activity, thus creating a functional vitamin K deficiency (**Figure 2**). Inadequate γ-carboxylation of vitamin K-dependent coagulation proteins interferes with the coagulation cascade, which inhibits blood clot formation. Large quantities of dietary or supplemental vitamin K can overcome the anticoagulant effect of vitamin K antagonists; thus, patients taking these drugs are cautioned against consuming very large or highly variable quantities of vitamin K (see Drug interactions). Experts now advise a reasonably constant dietary intake of vitamin K that meets current dietary recommendations (90-120 μg/day) for patients taking vitamin K antagonists like warfarin (9, 10).

Skeletal formation and prevention of soft tissue calcification

Vitamin K-dependent γ-carboxylation is essential to several bone-related proteins, including osteocalcin, anticoagulation factor protein S, matrix γ-carboxylated glutamate (Gla) protein (MGP), Gla-rich protein (GRP), and periostin (originally called osteoblast-specific factor-2). Osteocalcin (also known as bone Gla protein) is synthesized by osteoblasts (bone-forming cells); the synthesis of osteocalcin is regulated by the active form of vitamin D, 1,25-dihydroxyvitamin D (calcitriol). The calcium-binding capacity of osteocalcin requires vitamin K-dependent γ-carboxylation of three glutamic acid residues. Although its function in bone mineralization is not fully understood, osteocalcin is required for the growth and maturation of calcium hydroxyapatite crystals (see Osteoporosis) (11).

Protein S appears to play a role in the breakdown of bone mediated by osteoclasts. Individuals with inherited protein S deficiency suffer complications related to increased blood clotting, as well as osteonecrosis (12, 13). Protein S can bind and activate receptors of the TAM family that are involved in phagocytosis. Mutations in TAM receptors can result in visual impairment, defective spermatogenesis, autoimmune disorders, and platelet disorders (14).

MGP has been found in cartilage, bone, and soft tissue, including blood vessel walls, where it is synthesized and secreted by vascular smooth muscle cells. MGP is involved in the inhibition of calcification at various sites, including cartilage, vessel wall, skin elastic fibers, and the trabecular meshwork in the eye (see Vascular calcification) (15, 16). Moreover, several VKDPs, including MGP, have been associated with calcification sites in arteries, skin, kidneys, and eyes in certain inherited conditions, such as pseudoxanthoma elasticum and beta-thalassemia (17, 18).

The vitamin K-dependent proteins, GRP and periostin, are also synthesized in bone tissue, but their roles in bone metabolism are still unclear (19, 20). Expressed in normal human skin and vascular tissues, GRP has been colocalized with abnormal mineral deposits in the extracellular matrix in calcified arteries and calcified skin lesions (21). Expressed in most connective tissues, including skin and bone, periostin was initially associated with cell adhesion and migration. This VKDP also appears to promote angiogenesis (formation of new blood vessels) during cardiac valve degeneration and tumor growth (22, 23).

Current research suggests that reduced γ-glutamylcarboxylase activity and/or lower vitamin K bioavailability may impair the activity of VKDPs and contribute to bone mineralization defects and abnormal soft tissue calcification (see Disease Prevention) (24).

Regulation of cellular functions

Growth arrest-specific gene 6 protein (Gas6) is a vitamin K-dependent protein that was identified in 1993. It has been found throughout the nervous system, as well in the heart, lungs, stomach, kidneys, and cartilage. Identified as a ligand of the TAM family of transmembrane tyrosine kinase receptors, Gas6 appears to be a cellular growth regulation factor with cell-signaling activities. Gas6 has been involved in diverse cellular functions, including phagocytosis, cell adhesion, cell proliferation, and protection against apoptosis (5). It may also play important roles in the developing and aging nervous system (reviewed in 25). Further, Gas6 appears to regulate platelet signaling and vascular hemostasis (26). Expressed in most tissues and involved in many cellular functions, Gas6 has also been linked to several pathological conditions, including clot formation (thrombogenesis), atherosclerosis, chronic inflammation, and cancer growth (27-29).

Deficiency

Overt vitamin K deficiency results in impaired blood clotting, usually demonstrated by laboratory tests that measure clotting time. Symptoms include easy bruising and bleeding that may be manifested as nosebleeds, bleeding gums, blood in the urine, blood in the stool, tarry black stools, or extremely heavy menstrual bleeding. In infants, vitamin K deficiency may result in life-threatening bleeding within the skull (intracranial hemorrhage) (8).

Multiple biomarkers of vitamin K status exist (reviewed in 30), but only impaired blood coagulation is used as a measure of clinical vitamin K deficiency.

Adults

Vitamin K deficiency is uncommon in healthy adults for a number of reasons: (1) vitamin K is widespread in foods (see Food sources); (2) the vitamin K cycle conserves vitamin K (see Vitamin K oxidation-reduction cycle); and (3) bacteria that normally inhabit the large intestine synthesize menaquinones (vitamin K$_2$), although it is unclear whether significant amounts are absorbed and utilized (see Food sources). Adults at risk for vitamin K deficiency include those taking vitamin K antagonists and individuals with significant liver damage or disease (8). Additionally, individuals with fat malabsorption disorders, including inflammatory bowel disease and cystic fibrosis, may be at increased risk of vitamin K deficiency (31-34).

Infants

Newborn babies who are exclusively breast-fed are at increased risk for vitamin K deficiency because human milk is relatively low in vitamin K compared to formula. Newborn infants, in general, have low vitamin K status for the following reasons: (1) vitamin K transport across the placental barrier is limited; (2) liver storage of vitamin K is very low; (3) the vitamin K cycle may not be fully functional in newborns, especially premature infants; (4) the vitamin K content of breast milk is low, and immature gut flora (5, 35). Infants whose mothers are on anticonvulsant medication to prevent seizures are also at risk for vitamin K deficiency. Vitamin K deficiency in newborns may result in a bleeding disorder called vitamin K deficiency bleeding (VKDB) of the newborn (reviewed in 36). Because VKDB is life threatening and easily prevented, the American Academy of Pediatrics and a number of similar international organizations recommend that an intramuscular dose of phylloquinone (vitamin K$_1$) be administered to all newborns shortly after birth (reviewed in 37).

Controversies around vitamin K administration to newborns

Vitamin K and childhood leukemia: In the early 1990s, two retrospective studies were published suggesting a possible association between phylloquinone injections in newborns and the development of childhood leukemia and other forms of childhood cancer. However, two large retrospective studies in the US and Sweden, which reviewed the medical records of 54,000 and 1.3 million children, respectively, found no evidence of a relationship between childhood cancers and phylloquinone injections at birth (38, 39). Moreover, a pooled analysis of six case-control studies, including 2,431 children diagnosed with childhood cancer and 6,338 cancer-free children, found no evidence that phylloquinone injections for newborns increased the risk of childhood leukemia (40). In a policy statement, the American Academy of Pediatrics recommended that routine vitamin K prophylaxis for newborns be continued because VKDB is life threatening and the risks of cancer are unproven and unlikely (41). In the last decade, physicians have reported a rise in late-onset cases of VKDB due to an increasing trend of parental omission or refusal of newborn vitamin K prophylaxis (42, 43).

Lower doses of vitamin K$_1$ for premature infants: The results of two studies of vitamin K levels in premature infants suggest that the standard initial dose of phylloquinone (vitamin K$_1$) for full-term infants (1.0 mg) may be too high for premature infants (44, 45). These findings have led some experts to suggest the use of an initial phylloquinone dose of 0.3 mg/kg for infants with birth weights of less than 1,000 g (2 lbs, 3 oz), and an initial phylloquinone dose of 0.5 mg would probably prevent hemorrhagic disease in newborns (44). Yet, additional studies are needed to determine the best vitamin K prophylaxis in premature infants (46).

The Adequate Intake (AI)

In 2001, the US Food and Nutrition Board (FNB) of the Institute of Medicine (now the National Academy of Medicine) established the adequate intake (AI) level for vitamin K based on phylloquinone intake levels in healthy individuals (**Table 1**). The AI for infants was based on estimated intake of vitamin K from breast milk (47). The FNB did not consider menaquinone intakes; data on menaquinone consumption are limited (48).

Table 1. Adequate Intake (AI) for Vitamin K

Life Stage	Age	Males (μg/day)	Females (μg/day)
Infants	0-6 months	2.0	2.0
Infants	7-12 months	2.5	2.5
Children	1-3 years	30	30
Children	4-8 years	55	55
Children	9-13 years	60	60
Adolescents	14-18 years	75	75
Adults	19 years and older	120	90
Pregnancy	18 years and younger	-	75
Pregnancy	19 years and older	-	90
Breast-feeding	18 years and younger	-	75
Breast-feeding	19 years and older	-	90

Disease Prevention

Osteoporosis

The discovery of vitamin K-dependent proteins in bone has led to research on the role of vitamin K in maintaining bone health.

Vitamin K and bone health: observational studies

Vitamin K$_1$: Observational studies have found a relationship between phylloquinone (vitamin K$_1$) and age-related bone loss (osteoporosis). The Nurses' Health Study followed more than 72,000 women for 10 years. In an analysis of this cohort, women whose phylloquinone intakes were lower than 109 micrograms/day (μg/day) had a 30% higher risk for hip fracture compared to women with intakes equal to or above 109 μg/day (49). Another prospective study in over 800 elderly men and women, followed in the Framingham Heart Study for seven years, found that participants with dietary vitamin K intakes in the highest quartile (median, 254 μg/day) had a 65% lower risk of hip fracture than those with intakes in the lowest quartile (median, 56 μg/day) (50). Osteoporotic fractures are often linked to a reduction in bone mineralization. Yet, the investigators found no association between dietary phylloquinone intake and bone mineral density (BMD) in the Framingham subjects (50). While other studies failed to observe associations between dietary phylloquinone intake and measures of bone strength, BMD, or fracture incidence (51, 52), the cross-sectional study of a cohort of 3,199 middle-aged women found that subjects in the highest quartile of dietary phylloquinone intake had significantly greater hip and lumbar spine BMD than those in the lowest quartile (102 μg/day vs. 59 μg/day) (53). Moreover, cross-sectional and case-control studies have reported associations between higher phylloquinone intakes and lower incidence of hip fracture (54, 55).

However, because green leafy vegetables are the primary dietary source of phylloquinone and because they are usually part of a balanced diet, high phylloquinone consumption may simply be an indicator of healthy eating habits, which may — rather than phylloquinone itself — account for all or part of the association reported in observational studies (56).

The few studies that measured plasma phylloquinone generally found that higher circulating levels were associated with lower fracture risk (15, 57, 58). For example, the incidence of vertebral fractures was inversely correlated with lumbar BMD and plasma phylloquinone in a four-year prospective study that included 379 Japanese women ages 30-88 years (57). Yet, observational studies are not designed to making causal inferences, and only randomized controlled trials can evaluate whether phylloquinone may have beneficial effects on bone health (see Vitamin K supplementation studies and osteoporosis).

Vitamin K$_2$: There are few studies on associations between menaquinones (vitamin K$_2$) and bone health, perhaps because of the limited number of dietary sources of menaquinone-4 (MK-4), the main form of vitamin K$_2$ present in Western diets. The Japanese food natto, made of cooked soybeans fermented by *Bacillus subtilis natto*, is rich in MK-7. In a prospective cohort study that followed 944 Japanese women (ages 20-79 years), total hip BMD at baseline was positively associated with natto intake in postmenopausal women (59). During the three-year follow-up period, the rate of BMD loss at the femoral neck was significantly lower in women consuming natto (>200 μg/day of MK-7) compared to non-consumers. No association was found between natto intake and BMD in premenopausal women (59).

Total hip and femoral neck BMD was also reportedly higher in nearly 2,000 Japanese men aged 65 years and older who regularly consumed at least of one pack per day of natto (≥350 μg/day of MK-7) compared to those consuming less than one pack per week (<50 μg/day of MK-7) (60). Yet, increasing natto consumption also maximizes the intake of other dietary compounds (e.g., soy isoflavones) that have potential benefits for skeletal health; thus, there is need to find reliable measures of vitamin K status. To date, observational studies have failed to unequivocally support an association between circulating menaquinone (MK-7 and MK-4) levels and fracture risk (15, 61).

A meta-analysis that pooled the results of four prospective cohort studies and one nested case-control study found higher total dietary vitamin K intakes to be associated with a lower risk of total fracture (RR, 0.78; 95% CI: 0.56, 0.99) (62). In a recent Japanese cohort study not included in this meta-analysis (i.e., the Murakami Cohort Study), a protective association of dietary vitamin K intake was seen for vertebral fractures (p=0.005); vitamin K intake was not associated with total fracture in women or with either vertebral or total fracture in men (63).

Biomarker of vitamin K status and bone health

Total circulating levels of the bone protein, osteocalcin (OC), have been shown to be sensitive markers of bone formation. Several hormones and growth factors, including vitamin D but not vitamin K, regulate osteocalcin synthesis by osteoblasts. However, vitamin K is an essential cofactor for the γ-carboxylation of three glutamic acid residues in osteocalcin. Undercarboxylation of osteocalcin in human bone and serum has been linked to poor vitamin K status. The degree of osteocalcin γ-carboxylation is responsive to vitamin K nutritional interventions, and thus is used as a relative indicator of vitamin K status (11).

Circulating levels of uncarboxylated osteocalcin (ucOC) were found to be higher in postmenopausal women than premenopausal women and markedly higher in women over the age of 70. Also, high ratios of ucOC to total OC (ucOC/OC) appear to be predictive of hip fracture risk in elderly women (64, 65). Although vitamin K deficiency would seem the most likely cause of elevated blood ucOC/OC ratio, some investigators have documented an inverse relationship between biochemical measures of vitamin D nutritional status and ucOC levels, as well as a significant lowering of ucOC/OC ratio by vitamin D supplementation (66). It has been suggested that increased circulating ucOC/OC ratio could reflect a poor overall nutritional status that would include vitamin D inadequacy, which would explain the above-mentioned observations (67). However, in several randomized, placebo-controlled intervention studies conducted in young girls (67, 68) and postmenopausal women (69), vitamin D supplementation failed to decrease ucOC/OC ratios or show any additive effect on ucOC/OC lowering by supplemental vitamin K.

Vitamin K supplementation studies and osteoporosis

Vitamin K$_1$ supplementation: The review of five randomized clinical trials that assessed the effect of phylloquinone (vitamin K$_1$) supplementation on hip BMD using doses ranging from 200 μg/day to 5,000 μg/day for durations of 12 to 36 months found little promising benefit for bone health (15). Although supplementation with phylloquinone decreased ucOC levels in all five studies, only one study reported an effect of supplemental phylloquinone on BMD (70). In this study, 150 postmenopausal women were randomized to receive a placebo, minerals (500 mg/day of calcium, 150 mg/day of magnesium, and 10 mg/day of zinc) plus vitamin D (320 IU/day), or minerals, vitamin D, and phylloquinone (1,000 μg/day). The rate of BMD loss at the femoral neck, but not at the lumbar spine, was significantly lower in subjects with supplemental phylloquinone compared to the other two groups. Thus, evidence of a putative benefit of phylloquinone on bone health in older adults is considered weak. None of the studies were designed to assess the effect of phylloquinone on osteoporotic-related fractures. Further investigation may seek to evaluate whether phylloquinone supplementation could improve skeletal health in subjects at high-risk for vitamin K inadequacy (e.g., individuals with malabsorption syndromes or cystic fibrosis).

Vitamin K$_2$ supplementation: Pharmacological doses of menaquinone-4 (MK-4; brand name, menatetrenone) are currently used in Japan in the treatment of osteoporosis (71). Accordingly, most intervention trials investigating the effect of high-dose MK-4 on bone loss have been conducted in Japanese postmenopausal women. In a three-year placebo-controlled trial among postmenopausal women with osteopenia, adding a MK-7 supplement (375 μg/day) to combined calcium-vitamin D supplementation did not affect BMD or other bone health parameters despite reductions in serum ucOC (72). At present, the potential role for supplemental menaquinones on bone health still needs to be established in large, randomized, and well-controlled trials.

A 2019 systematic review and meta-analysis of clinical trials in postmenopausal women or women with osteoporosis found vitamin K supplementation — of any form — lowered risk of clinical fracture compared to controls (OR, 0.72; 95% CI, 0.55-0.95; 9 trials varying from 6 months to 2 years: 3 using phylloquinone, 5 using MK-4, and 1 using MK-7) (73). However, no benefit of vitamin K supplementation was seen for vertebral fractures (7 trials) or BMD (22 trials). The authors of this meta-analysis noted that the high heterogeneity of the included trials (i.e., form and dose of vitamin K, use of other supplements and drugs by participants, and treatment length) makes it difficult to inform clinical recommendations (73).

Vitamin K antagonists and bone health

Certain oral anticoagulants, such as warfarin, are known to be antagonists of vitamin K (see Coagulation). Few studies have examined chronic use of warfarin and risk of fracture in older women. One study reported no association between long-term warfarin treatment and fracture risk (74), while another one found a significantly higher risk of rib and vertebral fractures in warfarin users compared to nonusers (75). Additionally, a study in elderly patients with atrial fibrillation reported that long-term warfarin treatment was associated with a significantly higher risk of osteoporotic fracture in men but not in women (76). A meta-analysis of the results of 11 published studies found that oral anticoagulation therapy was associated with a very modest reduction in BMD at the wrist and no change in BMD at the hip or spine (77). The development of new anticoagulants that do not block vitamin K recycling may offer a safer alternative to the use of vitamin K antagonists (78).

Cardiovascular disease

Observational studies examining vitamin K intake in relation to cardiovascular-related mortality have found conflicting results (48). An inverse relationship between vitamin K intake and mortality was reported in a US national survey (NHANES III) of 3,401 participants (79). Adequate vs. inadequate vitamin K intakes (based on sex-specific AI: 90 μg/day for women and 120 μg/day for men) were associated with a 22% lower risk of cardiovascular disease (CVD)-related mortality and a 15% lower risk of all-cause mortality. The report also indicated that, while over two-thirds of individuals with chronic kidney disease had vitamin K intakes below the AI, the risk of CVD mortality was 41% lower in those with adequate compared to suboptimal intakes (79). However, higher vitamin K intakes were not associated with lower CVD mortality in a prospective study that followed 7,216 older adults at risk for developing CVD (80). This study associated higher intakes of phylloquinone, but not of menaquinones, with lower risk of all-cause mortality. More recently, in a prospective study that followed a cohort of 33,289 Dutch men and women for an average of 16.8 years (the EPIC-Netherlands), neither phylloquinone intake nor menaquinone intake at baseline was associated with mortality from cardiovascular disease, coronary heart disease, stroke, or all causes (81). Yet, a prospective study of 56,048 men and women participating in the Danish Diet, Cancer, and Health cohort reported higher phylloquinone intakes to be associated with lower risks of both cardiovascular disease-related mortality and all-cause mortality (82). Moreover, a few studies have examined the association of fasting circulating phylloquinone with cardiovascular-related or all-cause mortality. In a recent meta-analysis of individual participant data from three prospective cohort studies (the Multi-Ethnic Study of Atherosclerosis; the Health, Aging, and Body Composition Study, and the Framingham Offspring Study), a blood phylloquinone concentration less than or equal to 0.5 nmol/L (n=1,081) was associated with a 19% higher risk of all-cause mortality compared to a blood concentration >1.0 nmol/L (n=1,698; 83). This analysis did not find circulating phylloquinone to be linked with incident cardiovascular disease (83).

Observational studies offer limited support of an inverse relationship between phylloquinone intake and risk of incident cardiovascular disease, despite high intakes being sometimes regarded as a marker of healthy dietary habits associated with low cardiovascular risk (reviewed in 84). A prospective cohort study of 16,057 Dutch women (ages 49-70 years), followed for a mean period of 8.1 years, found a 9% reduction in risk for coronary heart disease (CHD) per each incremental 10 μg/day increase in menaquinone intake (85). In another earlier Dutch study that examined 4,807 healthy men and women 55 years and older, participants in the highest tertile of menaquinone intake (>32.7 μg/day) had a 41% lower risk of incident CHD and a 26% lower risk of all-cause mortality than those in the lowest tertile (<21.6 μg/day) (86). In addition, menaquinone intake was found to be inversely associated with aortic calcification, a major risk factor for CVD (86). A smaller prospective study among 2,987 Norwegian adults, followed for an average of 10.8 years, reported higher dietary intakes of vitamin K$_2$, but not of vitamin K$_1$, were associated with a lower risk of CHD (87). While these data are interesting, it is important to note that vitamin K$_2$ may solely be a marker of a heart-healthy diet and might not itself be cardioprotective. Most recently, the prospective Danish Diet, Cancer, and Health Study followed 53,372 older adults for an average of 21 years, finding both phylloquinone and menaquinone intake at baseline to be inversely associated with hospitalizations due to atherosclerotic cardiovascular events, including ischemic heart disease, ischemic stroke, and peripheral arterial disease (88).

Large-scale supplementation trials are needed to determine whether vitamin K$_1$ or vitamin K$_2$ reduces the risk of CHD or cardiovascular-related events like myocardial infarction or stroke.

Vascular calcification

One of the hallmarks of cardiovascular disease is the presence of atherosclerotic plaques in arterial walls. Plaque rupture that causes blood clot formation (thrombogenesis) is the usual cause of a myocardial infarction (heart attack) or stroke. While calcification of the plaques occurs as the atherosclerosis progresses, it is unclear whether calcification increases plaque instability and could predict risk of rupture and thrombogenesis (89). However, calcification may be predictive of future cardiovascular events, especially in those with chronic kidney disease (90). A meta-analysis of 30 prospective cohort studies, including a total of 218,080 participants, found that the presence of vascular calcification was associated with an overall three- to four-fold increased risk of cardiovascular events and mortality (91). An early population-based study of postmenopausal women (ages, 60-79 years) observed that the younger women (60-69 years) with aortic calcifications had lower vitamin K intakes than those without aortic calcifications, but this was not true for older women (70-79 years) (92). A prospective cohort study in 807 men and women, 39-45 years of age, did not find any correlation between dietary phylloquinone intake and coronary artery calcification, as measured non-invasively by computed tomography (93). Additionally, neither phylloquinone nor menaquinone intake was associated with calcification of breast arteries in a cross-sectional study of 1,689 women ages 49-70 years (94). However, in another cross-sectional study, the upper *vs.* lowest quartile of menaquinone (MK-4 to MK-10) intake (median intakes, 48.5 μg/day vs. 18 μg/day) was found to be associated with a 20% reduced prevalence of coronary artery calcification in 564 postmenopausal women (95).

Research has uncovered possible mechanisms by which vitamin K may inhibit mineralization (calcification) of vessels while promoting bone mineralization. The potential mechanisms, although not yet fully understood, implicate vitamin K-dependent proteins, including matrix Gla protein (MGP), Gla-rich protein (GRP), and Gas6 (96-98). Secreted by various cell types, such as vascular smooth muscle cells (VSMCs) in arterial vessel walls, MGP appears to be important for the prevention of calcification of soft tissues, including cartilage, vasculature, skin, and trabecular meshwork cells in the eye (15, 99). In MGP knockout mice, conversion of VSMCs into bone-like cells and extensive vessel calcification results in large vessel rupture and premature death. In humans, defective *MGP* gene has been linked to Keutel syndrome, a rare inherited condition characterized in particular by abnormal cartilage calcification and pulmonary artery stenosis (narrowing). Calcification prevention by MGP involved several mechanisms, including the binding to calcium crystals and the inhibition of proteins (bone morphogenic proteins; BMPs) known to promote ectopic bone formation (reviewed in 100).

Calcium-binding activity of MGP is regulated by two types of modifications (known as post-translational modifications since they take place after protein synthesis): the vitamin K-dependent carboxylation of up to five Glu residues and the phosphorylation of serine residues. A variation in the sequence (polymorphism) of the gene for MGP leading to a threonine-to-alanine transition in one of the five Gla domains of the protein may possibly prevent carboxylation and elicit a change in MGP ability to bind calcium. This polymorphism, known as *MGP*Thr83Ala, has been associated with the progression of coronary artery calcification over a mean period of 10.6 years in a community-based prospective study that followed 605 middle-aged men and women (101). This association was only observed among participants without detectable calcification at baseline and not in those who had baseline calcification (101). Interestingly, *MGP*Thr83Ala was also associated with higher risk of myocardial infarction and femoral artery calcification in carriers of the genotype (102).

Additionally, a small study initially found that, while undercarboxylated MGP (ucMGP) was absent from the innermost lining of the carotid arteries in healthy subjects, the majority of MGP in the carotid arterial lining of patients with atherosclerosis was undercarboxylated (103). In another study that examined the association between circulating MGP and incident cardiovascular events in 577 older men and women followed for a mean period of 5.6 years, the risk of cardiovascular disease (i.e., coronary heart disease, peripheral arterial disease, and cerebrovascular disease) was two- to three-fold greater in subjects in the highest *vs.* lowest tertile of plasma dephosphorylated and undercarboxylated MGP (dp-ucMGP) (104). The results of another prospective study suggested that circulating dp-ucMGP may be predictive of mortality risk in subjects with overt vascular disease (105). Indeed, the risk of cardiovascular-related and all-cause mortality was found to be nearly doubled in subjects with coronary artery disease or stroke in the highest *vs.* lowest quartile of dp-ucMGP concentrations (105).

Because suboptimal vitamin K nutritional status may limit carboxylation and result in biologically inactive ucMGP, it has been speculated that vitamin K supplementation may protect against vascular calcification. A three-year, double-blind, controlled trial investigated the potential effect of vitamin K on the progression of coronary calcification in 401 older, community-dwelling adults (ages, 60-80 years) free of cardiovascular disease at baseline (106). The participants were randomized to receive a daily multivitamin plus calcium and vitamin D with or without 500 mg of phylloquinone. Using measurements of coronary artery calcification at baseline and follow up, it was found that phylloquinone supplementation was able to limit the progression of vascular calcification and reduce plasma dp-ucMGP compared to control (106, 107). Although circulating dp-ucMGP was correlated to various markers of vitamin K status, no association with measures of coronary artery calcification were found (107). Smaller trials in those at high risk for coronary artery disease (108) or with existing aortic valve calcification (109), type 2 diabetes mellitus (110), or kidney disease (111, 112) have reported no benefit of vitamin K$_2$ supplementation on progression of vascular calcification. A meta-analysis of controlled clinical trials found that vitamin K supplementation reduced dp-ucMGP (7 trials), reduced ucOC (4 trials), and decreased progression of vascular calcification (3 trials) (113). Yet, the authors emphasize that any conclusions from their pooled analysis are limited by the high heterogeneity of the trials with respect to the form and dose of vitamin K utilized, as well as the assays that assessed vascular calcification (113).

Thus, further investigations are necessary to examine the role of other vitamin K-dependent proteins (e.g., GRP, periostin, Gas6) in human atherosclerotic plaque calcification and to evaluate the effect of supplemental vitamin K on the progression of vascular calcification and risk of cardiovascular disease.

Vitamin K antagonists and vascular calcification

Several cross-sectional studies have reported increased vascular calcium scores (a means to quantify vascular calcification) in chronic users of vitamin K antagonists compared to nonusers (reviewed in 114). Warfarin therapy has also been associated with higher circulating concentrations of dp-ucMGP in a prospective study that examined vascular calcification in subjects with cardiovascular disease (105). Newly developed direct inhibitors of coagulation factors that do not interfere with VKDP activity may be more suitable than vitamin K antagonists, especially with regards to vascular calcification (114).

Osteoarthritis

Osteoarthritis, a degenerative joint condition that affects more than 32 million US adults (115), is characterized by the breakdown of articular cartilage (i.e., cartilage within the joint). Because several vitamin K-dependent proteins are present in cartilage and in bone (116), vitamin K inadequacy may have a role in the development of osteoarthritis. A few observational studies have investigated a possible link between vitamin K intake or status and osteoarthritis. A cross-sectional study among 719 Japanese older adults found dietary intake of vitamin K to be inversely associated with knee osteoarthritis (117). In the Framingham Offspring Study (n=672; mean age, 66 years), higher plasma concentrations of phylloquinone were associated with a lower risk of hand, but not knee, osteoarthritis (118). A longitudinal study of 1,180 US adults (mean age, 62 years) found that low plasma concentrations of phylloquinone (≤0.5 nM) at baseline — indicative of a subclinical vitamin K deficiency — were associated with a 56% increase in risk of knee osteoarthritis after 30 months compared to those with higher plasma concentrations (119). In a more recent longitudinal study among 523 older US adults participating in the Health, Aging, and Body Composition Study, those with extremely low plasma concentrations of phylloquinone (<0.2 nM) at baseline had increased progression of knee osteoarthritis over three years, assessed by MRI of articular cartilage and the meniscus; those with higher plasma concentrations experienced no significant progression of knee osteoarthritis (120). Moreover, recent studies have associated use of the vitamin K antagonist drugs with higher risks of osteoarthritis (121) and joint replacement (121) of the knee and hip compared to nonusers.

While these observational data are interesting, randomized controlled trials are needed to determine whether vitamin K supplementation in those with low vitamin K status might help prevent or treat osteoarthritis. In an ancillary study of a double-blind, controlled trial examining the effects of vitamin K supplementation on bone loss and vascular calcification in older adults, no effects of phylloquinone supplementation (500 μg/day) were found on incidence of hand osteoarthritis after three years (122). Study participants were not screened for vitamin K status, and in a subgroup analysis, those with serum phylloquinone ≤1 nM at baseline that reached >1 nM at year 3 had less joint deterioration. These data infer that only those individuals with low vitamin K status benefit from vitamin K supplementation. Unfortunately, no measures were available for knee osteoarthritis, and it is well established that hand and knee osteoarthritis represent different phenotypes. Additional clinical trials that specifically examine the effect of vitamin K supplementation on osteoarthritis development are needed, especially in those with inadequate vitamin K status.

Sources

A US national survey, NHANES 2011-2012, found that average dietary intakes of vitamin K (all forms) vary greatly among individuals, with values ranging from 80 to 195 μg/day of phylloquinone for men and 78 to 223 μg/day of phylloquinone for women (123). Mean intakes for both men and women were 117 μg/day of phylloquinone; however, 57% of men and 37% of women did not meet the Adequate Intake (AI) level (123).

Food sources

Vitamin K$_1$

Phylloquinone (vitamin K$_1$) is the major dietary form of vitamin K in most diets. Green leafy vegetables and some plant oils (soybean, canola, olive, and cottonseed) are major contributors of dietary vitamin K. Mixed dishes have also been found to significantly contribute to vitamin K intake in the US (123). However, phylloquinone bioavailability from green vegetables is lower than from oil or supplements. Also, the phylloquinone content of green vegetables depends on their content in chlorophyll (green pigment), so that outer leaves have more phylloquinone than inner leaves. The efficiency of phylloquinone intestinal absorption varies among plant sources and is increased with the addition of a fat source to a meal. Finally, the hydrogenation of vegetable oils may decrease the absorption and biological effect of dietary phylloquinone (reviewed in 2, 9). If you wish to check foods for their nutrient content, including phylloquinone, search USDA's FoodData Central. A number of phylloquinone-rich foods are listed in **Table 2**, with their content in phylloquinone expressed in micrograms (μg).

Table 2. Some Food Sources of Phylloquinone

Food	Serving	Phylloquinone (μg)
Kale, frozen, boiled	1 cup	493
Chard, raw	1 cup	299
Parsley, raw	¼ cup	246
Broccoli, cooked	1 cup	220
Spinach, raw	1 cup	121
Watercress, raw	1 cup	85
Cabbage, green, raw	1 cup	68
Romaine lettuce, raw	1 cup	44
Soybean oil	1 Tablespoon	26
Canola oil	1 Tablespoon	10
Olive oil	1 Tablespoon	8
Cottonseed oil	1 Tablespoon	3

Vitamin K$_2$

Menaquinones (vitamin K$_2$) are primarily of microbial origins and thus commonly found in fermented foods, such as cheese, curds, and natto (fermented soybeans) (124, 125). MK-4 is the only menaquinone that is not produced by bacteria. MK-4 is formed from menadione (a synthetic form of vitamin K) found in animal feeds or is converted in a tissue-specific way from multiple dietary forms of vitamin K, including phylloquinone and various menaquinones (4, 126). Menaquinone-4 is found in dairy products, including milk, and in some meats (125). Longer chain menaquinones are found in limited fermented food products. The Japanese fermented soybean-based, natto, is rich in MK-7 (998 μg/100 g) and also contains MK-8 (84 μg/100 g). Some cheeses contain MK-8 and MK-9 (2, 125). Additionally, animal livers are a source of long-chain menaquinones (MK-7 to MK-13) (9).

Food composition databases, including USDA's FoodData Central, have limited data on menaquinone content in foods. Thus, menaquinone contribution to total vitamin K intakes is difficult to estimate and likely to vary between populations with different food consumption practices (2, 125). Bacteria that normally colonize the large intestine (colon) can synthesize menaquinones. It was initially thought that up to 50% of the human vitamin K requirement might be met by bacterial synthesis. However, all forms of vitamin K are absorbed in the small intestine via a mechanism requiring bile salts, while most of the menaquinone production takes place in the colon where bile salts are lacking. Current research suggests that the contribution of bacterial synthesis to vitamin K status is much less than previously thought, although the exact contribution remains unclear (16, 127).

Supplements

In the US, both phylloquinone and menaquinones are available without a prescription in multivitamin, single-nutrient, or multiple-nutrient supplements in varying doses; vitamin K content of multivitamins typically range from 20 to 120 μg per tablet (128). The US Food and Drug Administration (FDA) has not authorized any health claims for any forms of vitamin K.

Safety

Toxicity

Although allergic reactions are possible, there is no known toxicity associated with high doses (dietary or supplemental) of the phylloquinone (vitamin K$_1$) or menaquinone (vitamin K$_2$) forms of vitamin K (47). The same is not true for synthetic menadione (vitamin K$_3$) and its derivatives. Menadione can interfere with the function of glutathione, one of the body's natural antioxidants, resulting in oxidative damage to cell membranes. Menadione given by injection has induced liver toxicity, jaundice, and hemolytic anemia (due to the rupture of red blood cells) in infants; therefore, menadione is no longer used for treatment of vitamin K deficiency (5). No tolerable upper intake level (UL) has been established for vitamin K (47).

Nutrient interactions

Large doses of vitamin A and vitamin E have been found to antagonize vitamin K (8). Excess vitamin A appears to interfere with vitamin K absorption, whereas vitamin E may inhibit vitamin K-dependent carboxylase activity and interfere with the coagulation cascade (129). One study in adults with normal coagulation status found that supplementation with 1,000 IU/day of vitamin E for 12 weeks decreased γ-carboxylation of prothrombin, a vitamin K-dependent protein (130). Individuals taking anticoagulatory drugs like warfarin and those who are vitamin K deficient should not take vitamin E supplements without close medical supervision because of the increased risk of hemorrhage (excessive bleeding) (131).

Drug interactions

The anticoagulant effect of vitamin K antagonists (e.g., warfarin) may be compromised by very high dietary or supplemental vitamin K intake. Moreover, daily phylloquinone supplements of up to 100 μg are considered safe for patients taking warfarin, but therapeutic anticoagulant stability may be undermined by daily doses of MK-7 as low as 10 to 20 μg (132). It is generally recommended that individuals using warfarin try to consume the AI for vitamin K (90-120 μg/day) and avoid large fluctuations in vitamin K intake that might interfere with the adjustment of their anticoagulant dose (9, 10, 133). The prescription of anti-vitamin K anticoagulants, anticonvulsants (e.g., phenytoin), and anti-tuberculosis drugs (e.g., rifampin and isoniazid) to pregnant or breast-feeding women may place the newborn at increased risk of vitamin K deficiency (134).

The drug amiodarone, used in the management of certain cardiac arrhythmias (irregular heartbeat), including atrial fibrillation, can enhance the anticoagulant effect of warfarin and thus increase the risk of hemorrhage (135, 136). Further, the use of cholesterol-lowering medications (like cholestyramine and colestipol), as well as orlistat, mineral oil, and the fat substitute, olestra, may interfere with fat absorption and affect the absorption of fat-soluble vitamins, including vitamin K (137).

Linus Pauling Institute Recommendation

It is not clear whether the AI for vitamin K is enough to optimize the γ-carboxylation of vitamin K-dependent proteins in bone (see Osteoporosis). To consume the amount of vitamin K associated with a decreased risk of hip fracture in the Framingham Heart Study (about 250 μg/day) (50), an individual would need to eat a little more than ½ cup of chopped broccoli or a large salad of mixed greens every day. Though the dietary intake of vitamin K required for optimal function of all vitamin K-dependent proteins is not yet known, the Linus Pauling Institute recommends taking a multivitamin/mineral supplement and eating at least one cup of dark-green leafy vegetables daily. Replacing dietary saturated fats like butter and cheese with monounsaturated fats found in olive oil and canola oil will increase dietary vitamin K intake and may decrease the risk of cardiovascular disease.

Older adults (>50 years)

Because older adults are at increased risk of osteoporosis and hip fracture, the above recommendation for a multivitamin/mineral supplement and at least one cup of dark green leafy vegetables daily is especially relevant.

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